

A Randomised Controlled Trial
Comparing Two Methods of Providing
Volume Targeted Ventilation in Preterm Infants:
Volume Guarantee versus Volume-Controlled
Ventilation
The VoluVent Trial

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Abstract

Background: Many preterm infants require mechanical ventilation via an endotracheal tube for the treatment of neonatal respiratory distress (RDS). A side effect of mechanical ventilation is lung injury. VTV aims to reduce lung injury by controlling the tidal volumes delivered to the infant by the ventilator. Many VTV modes are widely in use but have not been compared using clinically relevant outcomes.

Aim: This was the first trial to compare two modes of VTV in preterm infants with RDS. We aimed to compare volume-controlled ventilation (VCV) with volume guarantee (VG) using clinically relevant outcomes.

Hypothesis: We hypothesised that, in preterm infants with RDS, the time taken to be ready for extubation would be shorter in the VG group compared with VCV. The initial sample size calculation indicated that 102 infants were needed to show a 33% reduction in the time taken to be ready for extubation with a significance level of 0.05 and a power of 80%.

Methods: This single centre, randomised controlled pilot trial was undertaken in a tertiary neonatal unit from July 2013 – December 2015. Infants were stratified into two groups according to gestational age at birth (<28 weeks' gestation and 28 – 33+6 weeks' gestation). The primary outcome was the duration of time from starting the trial mode until being ready for extubation. Readiness for extubation was defined using pre-determined 'success' criteria. Secondary outcomes included important clinical outcomes. After four months the consent method was changed from prospective to deferred parental consent.

A trial oversight review of data from the first 50 infants identified that the primary outcome data were not likely to be normally distributed. The statistical analysis plan was therefore updated prior to any data analysis. We planned to present data as descriptive summary statistics including survival probabilities, hazard ratios (HRs) and odds ratios (ORs). In addition, using early phase trials statistical methods, a difference of 15% between groups in the numbers of infants reaching the 'success' criteria at 48 hours would indicate a potentially significant difference between groups.

An ancillary study was undertaken using mechanistic data downloaded from ventilators to validate one of the 'success' criteria (mean airway pressure).

Results: One hundred and thirteen infants were enrolled. One infant was subsequently withdrawn due to a diagnosis consistent with exclusion criteria. The median time to 'success' criteria was 23 hours (95% CI 10.78 – 35.22 hours) in the VG group and 36 hours (95% CI 18.03 – 53.97) in the VCV group. The HR was 0.93 (95% CI 0.63 – 1.37). Thirty four infants in the VG group and 33 infants in the VCV group had met the 'success' criteria by 48 hours. Subgroup analyses showed that, in infants born at 28 – 33+6 weeks' gestation, the median time to reach the primary outcome faster in the VG group. The pneumothorax rates and duration of ventilation were lower in the VG group. The use of deferred consent appeared to be more acceptable to parents and led to an improvement in the recruitment rate.

The ancillary study showed very good correlation between the mean airway pressure values recorded manually once every hour and the values downloaded with every breath. This validated the use of manual recordings of mean airway pressure as part of the primary outcome.

Conclusions: There was a clinical important difference between VG and VCV in the time taken for infants to be ready for extubation. This difference favoured VG but a larger trial is needed to show a definitive result. This trial also highlights current gaps in knowledge regarding short-term clinical outcomes and the use of VTV modes in different subgroups of infants. Deferred consent appears to be acceptable to parents of newborn infants but qualitative research is needed to explore this further.

This thesis describes The VoluVent Trial (ISRCTN 04448562), the first clinical trial to compare two types of volume-targeted ventilation (VTV) in preterm infants. One of the known side effects of mechanical ventilation is lung injury. VTV aims to minimise ventilator-associated lung injury and different types of VTV are used widely. However, there is no evidence to confirm whether one type of VTV is better than another for preterm infants.

Dedication

This is dedicated to my family; to my sisters, Sarah and Clare, and my parents, Gerry and Roger, who have supported me through many ups and downs and who have always believed in me.

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There are many people whom I would like to acknowledge and thank with regards to this thesis.

First and foremost, I would like to thank the parents and babies who participated in The VoluVent Trial. Without the altruistic willingness of the parents to give consent, this trial would not have been possible. They agreed to their babies' participation in the trial at an extraordinarily difficult time of their lives and I cannot thank them enough for this.

I am deeply grateful to my supervisory team for their constant support, expertise, time and mentorship. Professor Sunil Sinha and Professor Win Tin provided never-ending guidance, wisdom and practical support on all aspects of the trial and thesis from start to finish. Professor Josef Vormoor was instrumental in providing academic oversight and review of my academic training. Dr Rachel Agbeko provided encouragement and reflective insight into many aspects of my academic training and clinical research. Professor Deborah Stocken provided her expertise in statistical approaches and trials methodology, and supported me in learning about statistics for clinical research. There is not enough room here to describe their kindness and all that they have done for me. I offer them all my sincerest thanks.

Others whom I would specifically like to thank are: Dr Nina Wilkinson and Dr Jaideep Singh for undertaking the trial oversight review; Dr John Allen and Ms Audrey MacDonald for their advice and assistance in signal processing and generation of 'M3' data (see Declarations section); Dr Tony Roberts for generating the computerised randomisation sequence and preparing the randomisation envelopes; Mr Andreas Lissberg, Mr Tom Leenhoven and Mr Hilbert Koetsier for providing advice on, and the license for, the use of the VOXP Research Data Collector; Dr Charlotte Kemp for advice on data analysis and Dr Fiona Wood for support with the initial sample size calculation; Professor Peter Davis for advice on co-enrolment; Professor Samir Gupta for reviewing the trial protocol; Dr Henk Jongschaap for providing radiological opinion on chest x-rays; Mr Mark Green for providing regional clinical data from the Northern Neonatal Network reports; and Dr Eleanor Smith for proof-reading the final draft of this thesis.

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Declaration

The M3 data described in the ancillary study in Chapter 5 of this thesis were collected by myself as digital data using VOXP Research Data Collector software (Applied Biosignals, GmbH, Germany). They were converted to airway pressure waveforms by Ms Audrey MacDonald (Northern Medical Physics and Clinical Engineering, Freeman Road Hospital, Newcastle upon Tyne) using MATLAB software (MATLAB 2012a, The MathWorks, Inc., Natick, Massachusetts, United States). Ms Macdonald used these waveforms to calculate the 'moving average' airway pressure data that made up the M3 values. Dr John Allen (Northern Medical Physics and Clinical Engineering, Freeman Road Hospital, Newcastle upon Tyne) provided advice on signal analysis for the ancillary study. I thank Ms MacDonald and Dr Allen for their assistance in this regard.

Otherwise, all the work described in this thesis, including design and implementation of the trial, ethical and regulatory approvals, and statistical analyses, is my own.

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Abbreviations

A/C	assist/control
Baby-OSCAR	Outcome after Selective Early Treatment for Closure of Patent Ductus Arteriosus in Preterm Babies (Baby-OSCAR trial)
BPD	bronchopulmonary dysplasia
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CPAP	continuous positive airway pressure
CRASH-2	Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2 trial)
CSF	cerebrospinal fluid
DART	Dexamethasone: A Randomised Trial
EDD	estimated date of delivery
ELBW	extremely low birth weight
ELFIN	a multi-centre randomised placebo-controlled trial of prophylactic enteral lactoferrin supplementation to prevent late-onset invasive infection in very preterm infants
ETT	endotracheal tube
FiO ₂	fraction of inspired oxygen
g	grams
GBS	Group B Streptococcus
H ₂ O	chemical formula for water (unit used for airway pressure measurements)
HFOV	high frequency oscillatory ventilation
HHFNC	humidified high flow nasal cannula

HIPSTER	A multicentre, randomised controlled, non-inferiority trial, comparing high flow therapy with nasal continuous positive airway pressure as primary support for preterm infants with respiratory distress (HIPSTER trial)
HR	hazard ratio
IMV	intermittent mandatory ventilation
IQR	interquartile range
IRAS	Integrated Research Application System
ISRCTN	International Standard Randomised Controlled Trial Number
IVH	intraventricular haemorrhage
JSNA	Joint Strategic Needs Assessment
kg	kilogram
kPa	kilopascals
LSCS	lower segment caesarian section
MAP	mean airway pressure
MHRA	Medicines and Healthcare products Regulatory Agency
MIB	medical information bus
mls	millilitres
MRC	Medical Research Council
n	number
NEC	necrotising enterocolitis
NHS	National Health Service
NICU	neonatal intensive care unit
NiDOP	Non-invasive Doppler or Oscillometric Pressure study
NIPPV	Non-invasive positive pressure ventilation
NIV	non-invasive ventilation
°C	degrees Celsius

OR	odds ratio
PCV	pressure control ventilation
PEEP	positive end expiratory pressure
PDA	patent ductus arteriosus
PICU	paediatric intensive care unit
PIE	pulmonary interstitial emphysema
PIP	peak inspiratory pressure
PlaNeT-2	Platelets for Neonatal Transfusion - Study 2
PLV	Pressure-limited ventilation
PPROM	prolonged preterm rupture of membranes
PRVC	pressure-regulated volume control
PSV	pressure support ventilation
PSV+VG	pressure support ventilation plus volume guarantee
PTPdi	transdiaphragmatic pressure time product
PVL	periventricular leukomalacia
RCT	randomised controlled trial
R+D	Research and Development
RDS	respiratory distress syndrome
ROP	retinopathy of prematurity
SAE	serious adverse event
SAP	statistical analysis plan
SBT	spontaneous breathing test
SD	standard deviation
SiFT	Speed of Increasing milk Feeds study
SIMV	synchronised intermittent mandatory ventilation
SIMV+PSV	synchronised intermittent mandatory ventilation plus pressure support ventilation

SUSAR	suspected unexpected serious adverse event
TCPL	time-cycled pressure-limited
VALI	ventilator-associated lung injury
VAPS	volume-assured pressure support
VCV	volume-controlled ventilation
VG	volume guarantee
VILI	ventilator-induced lung injury
VTV	volume-targeted ventilation

Outputs from this study

Awards

- The Richard D. Rowe Clinical Research Award, awarded by the Society for Pediatric Research for presentation of The VoluVent Trial, the Pediatric Academic Societies Meeting, San Francisco, May 2017

Publications

- **Chitty H**, Agbeko R. (2015) 'Book Review: Pediatric and Neonatal Mechanical Ventilation: From Basics to Clinical Practice'. *Seminars in Fetal and Neonatal Medicine*, 20(5), pp.373
- **Chitty H**, Sinha S. (2015) 'Volume-targeted ventilation in newborn infants', *Infant*, 11(1), pp.1-5

Platform presentations

- **Chitty HE**, Tin W, Agbeko R, Stocken D, Vormoor J, Sinha S. Volume controlled or Volume Guarantee ventilation in preterm infants: A Randomised Controlled Trial. 2nd Congress of joint European Neonatal Societies, Venice, November 2017.
- **Chitty HE**, Tin W, Agbeko R, Stocken D, Vormoor J, Sinha S. A Randomised Controlled Trial Comparing Two Types of Volume-Targeted Ventilation in Preterm Infants with Respiratory Distress Syndrome. Pediatric Academic Societies, San Francisco, May 2017
- **Chitty HE**, Tin W, Agbeko R, Stocken D, Vormoor J, Sinha S. Presentation of the protocol: The VoluVent Trial - A Randomised Controlled Trial Comparing Two Types of Volume-Targeted Ventilation for Preterm Infants with Respiratory Distress Syndrome. Northern Paediatric Research and Development Conference, Health Education England North East, March 2015

Invited platform presentations

- **Chitty HE**. Emerging New Evidence for Volume-Targeted Ventilation in Neonates. REaSoN Neonatal Meeting, Warwick, UK, July 2017

- **Chitty HE**. Newer Evidence for Volume-Targeted Ventilation: The VoluVent Trial. Annual International Neonatal Conference, Middlesbrough, UK, June 2017
- **Chitty HE**. The VoluVent Study. Advances in Respiratory Support of the Newborn, 2nd Annual Respiratory Symposium, Cambridge, UK, May 2017

Poster presentations

- **Chitty HE**, Tin W, Agbeko R, Stocken D, Vormoor J, Sinha S. A Randomised Controlled Trial Comparing Two Types of Volume-Targeted Ventilation in Preterm Infants with Respiratory Distress Syndrome. Royal College of Paediatrics and Child Health Annual Conference, Birmingham, May 2017
- **Chitty H**, Tin W, Sinha S, Agbeko R, Stocken D, Vormoor J. Presentation of the protocol: Complex Interventions Research in Neonatal Intensive Care: A Randomised Controlled Trial Comparing Two Methods of Volume-Targeted Ventilation in Preterm Infants, Newcastle Academic Health Partners Inaugural Conference, Newcastle University, June 2016

Professional groups

- One of 32 stakeholders who reviewed and developed draft guidance on deferred consent in paediatric and neonatal research at the Medical Research Council Hubs for Trial Methodology Research guidance development meeting in Liverpool, 23rd July 2014. This guidance formed part of a published document entitled 'Research without prior consent (deferred consent) in trials investigating the emergency treatment of critically ill children: CONNECT study guidance', version 2 updated July 2015, (written and published by the CONNECT advisory group, Liverpool University, MRC Hubs for Trials Methodology Research and the Wellcome Trust).
- Participated in The COVenT (Core Outcomes in Ventilation Trials) study Delphi survey (part of the COMET initiative, MRC North West Hub for Trials Methodology).

- Participated in the COIN (Core Outcomes in Neonatology) study Delphi survey (part of the COMET initiative, MRC North West Hub for Trials Methodology).
- Founder and Chair of the Northern Neonatal Network Annual Research Meeting, 2015 – present.
- Chair of the Teesside Paediatric and Neonatal Research Group, 2013 – 2016.

Chapter 1 Introduction

Survival rates for preterm infants have improved over time (Costeloe et al., 2012, Younge et al., 2017). Extremely small and preterm infants are now surviving due to improvements in antenatal, perinatal and neonatal care (Walsh et al, 2011). However preterm infants are born with organs that are under-developed. Their organ systems are often not able to function adequately without the support of nursing, medical and parental care combined with mechanical devices and technology. This is known as neonatal intensive care. Preterm infants may require days, weeks and even months of neonatal intensive care in order to grow and develop to a point where they can survive without this level of care.

One such organ system in preterm infants is the respiratory system. In basic terms, this consists of the upper and lower airways, the lung tissue (parenchyma), and the supporting muscles, bones and connective tissue. The respiratory system is integrally linked to all of the other organ systems, including the heart and circulation, the gastrointestinal system, the immune system and the brain and nervous system. A preterm infant's survival depends on the adequate and inter-dependent functioning of all of these organ systems.

In order to support a preterm infant's respiratory system mechanical ventilation via an endotracheal (breathing) tube may be needed. This involves the placement of the endotracheal tube (ETT) into the trachea (windpipe) and then connection of the ETT to a ventilator. The ventilator can support the infant's spontaneous breathing or can provide artificial respiration if the infant is not breathing. Although this is often a life-saving treatment, one side effect of mechanical ventilation is injury to the lungs. Therefore there is a balance to strike between using mechanical ventilation to sustain life whilst minimising the duration of its use in order to minimise lung injury.

This thesis focuses on a randomised controlled trial comparing two types (modes) of ventilation that are used with the aim of minimising lung injury in preterm infants. Although these modes are used widely (Klingenberg et al., 2011a) this is the first trial to compare two such modes in preterm infants using outcomes that reflect potential lung injury.

Introduction: Chapter 1 introduces the thesis and the trial which was called The VoluVent Trial (ISRCTN registry number 04448562). It frames the trial in its context as a research study of complex emergency interventions in a neonatal intensive care unit.

Background: Chapter 2 discusses the rationale for the trial. It describes lung disease associated with prematurity, ventilator-associated lung injury, and the published literature on volume-targeted ventilation (VTV) in newborn infants. Three large reviews of published literature (McCallion et al., 2005; Wheeler et al., 2010; Klingenberg et al., 2017) have shown better clinical outcomes in infants who received VTV compared with pressure-limited ventilation. However, there are no published studies comparing different types of VTV in preterm infants. This trial was, therefore, undertaken to address this gap in knowledge.

Method: Chapter 3 describes the methods used to undertake this randomised controlled pilot trial. The trial compared two modes of VTV, volume-controlled ventilation (VCV) and volume guarantee (VG), in preterm infants with respiratory distress syndrome. This involved the design of a rigorous but pragmatic trial aimed at achieving meaningful results whilst ensuring it could be carried out in a busy intensive care unit. A process evaluation was also planned for certain aspects of the trial. The challenges posed by the initial methodology, including the consent process and the sample size, are explained in this chapter. The detailed statistical analysis plan is described, the full version of which is included in the Appendices.

Results: Chapter 4 describes the results of The VoluVent Trial in detail. Initial recruitment problems were encountered. However a change to the consent process improved recruitment and appeared to be more appropriate for parents of newborn infants receiving emergency treatments. The primary and secondary outcome data and the serious adverse events were analysed according to the statistical analysis plan and are presented in this chapter. Covariates and compliance with the protocol are also described. This trial showed a clinically relevant difference between VCV and VG in the primary outcome measure. Its findings highlight areas for further research.

Ancillary study: Chapter 5 describes an ancillary study undertaken during the trial as part of the process evaluation. The airway pressures were downloaded

'in real time' from the ventilators of infants in The VoluVent Trial. These values were compared with the manually recorded mean airway pressure values that formed part of the trial's primary outcome measure. This chapter describes the planned methodology, the statistical analysis plan, the results of this study, and its strengths and limitations.

Consent during research into emergency interventions: Implementing the most appropriate consent process for an intensive care trial was an important challenge encountered during The VoluVent Trial. Chapter 6 discusses the lessons learnt from the trial about the ethical and practical challenges in seeking informed consent during neonatal research. It focuses particularly on consent for research into emergency interventions in infants and children. Recent literature regarding consent in such settings is discussed and the current gaps in knowledge are outlined.

Discussion: Chapter 7 discusses the results of The VoluVent Trial and its ancillary study. It describes the strengths and limitations of the trial and the lessons learnt from the process evaluation. This chapter discusses the contribution made by The VoluVent Trial to current scientific knowledge. The unique data gained from the trial and the recommendations for future research have already been recognised internationally and will provide the basis for a larger trial. The remaining gaps in knowledge and recommendations as to how some of these might be addressed in future are also discussed.

Conclusion: Chapter 8 provides a summary of this thesis, bringing together the themes of the use of VTV in preterm infants and how best to investigate its use in an intensive care setting.

Chapter 2 Literature review

2.1 Introduction

Lung injury in preterm infants is multifactorial in origin. The causative factors often co-exist and may exacerbate each other (Attar et al., 2002). Some of these factors, particularly the inflammatory factors, occur before delivery (Jobe et al., 1998). Preterm birth results in the abrupt cessation of fetal lung development and this underlies the lung disease associated with prematurity (Jobe et al., 2000). The ensuing clinical management strategies required to treat preterm lung disease can also contribute to its sequelae if they are not used judiciously (Jobe, 2011).

One manifestation of respiratory failure in newborn infants is respiratory distress syndrome (RDS) (Donn et al., 2017b). Respiratory failure, including RDS, can lead to the requirement for mechanical ventilation. Mechanical ventilation is a treatment associated with lung injury and closely inter-linked with the other causes of lung injury in preterm infants, such as oxygen (Jobe et al., 2017). The consequence of lung injury in preterm infants is bronchopulmonary dysplasia (BPD), a condition that can have significant long-term clinical and financial effects for the infant and their family (Gibson et al., 2015).

Therefore, preventing or limiting lung injury in preterm infants is important. Mechanical ventilation can be a necessary and life-saving treatment for neonates with respiratory failure for whom non-invasive respiratory support is not adequate or appropriate. (Sinha SK et al., 2011). There is much published literature on neonatal ventilation and comparisons of ventilatory techniques. Results of recent reviews favour the use of volume-targeted ventilation (VTV) for preterm infants with RDS (Wheeler et al., 2011; Peng et al., 2014; Klingenberg et al., 2017). VTV is now used widely (Klingenberg et al., 2011). The authors of the two most recent Cochrane reviews (Wheeler et al., 2010, Klingenberg et al., 2017) made recommendations for further research, including the recommendation that different volume-targeting strategies should be compared. This review summarises the evidence behind the use of VTV in newborn infants. The clinical outcomes that have been studied and the effects of different volume-targeted modes on these outcomes will be discussed, as well as the current gaps in knowledge.

2.2 Pulmonary mechanics

The “pulmonary injury sequence” associated with lung injury in preterm infants was described by Attar and Donn (Attar et al., 2002). This is demonstrated as a timeline in Figure 2-1.

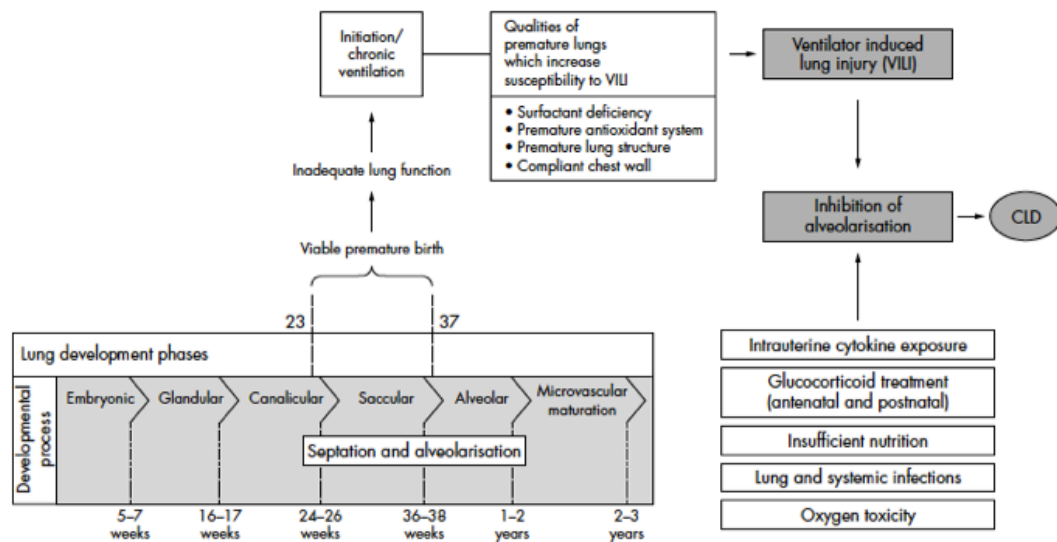


Figure 2-1 The “pulmonary injury sequence” (taken from Attar et al., 2002)

The development of alveoli, the units of lung responsible for gas exchange, is known as alveolarisation (Joza et al., 2015). Alveolarisation can start as early as 28 weeks' post-conception and continues for months or even years into postnatal life. In fact, much of the process of alveolarisation occurs after 36 weeks of gestation (Jobe., 2011), highlighting the fact that very or extremely preterm infants have very little pulmonary architecture at the time of birth. Preterm birth halts fetal lung development. Lung injury then follows due to the imposition of factors demonstrated in Figure 2-1. This leads to interrupted alveolarisation by which postnatal lung development is delayed or deviated down a different developmental pathway (Jobe, 2011).

Antenatal insults such as exposure to infection or pro-inflammatory cytokines before birth can precipitate lung injury in the newborn. Infants who have been exposed to such mediators in utero and then require respiratory interventions after birth may then experience a cumulative effect of injury mediators (Jobe, 1999).

2.3 Respiratory failure in preterm newborn infants

2.3.1 Causes of respiratory failure

Respiratory failure can occur in infants of any gestation. It is much more common in preterm infants due to the arrested alveolarisation described above. Some causes are similar in preterm and term infants whilst others tend to occur in one group rather than the other. This review focuses on respiratory failure in preterm infants.

2.3.2 Respiratory distress syndrome

Respiratory distress syndrome (RDS) is a common cause of respiratory failure in preterm infants (Hamvas, 2011). It occurs in approximately 80% of infants born at 24 weeks' of gestation (extremely preterm) and even 5% of infants born at 36 weeks' gestation (late preterm) (Donn et al., 2017b).

The underlying causes of RDS are multifactorial. Preterm infants are predisposed to RDS due to a combination of:

- immaturity of lungs, pulmonary vasculature, respiratory muscles and nervous system (Spitzer et al., 2011),
- surfactant immaturity and deficiency (Jobe, 2006),
- reduced pulmonary compliance and increased chest wall and airway compliance (Spitzer et al, 2011),
- increased diffusion distance for gas exchange (Jobe, 2006).

2.3.3 Clinical features of RDS

RDS is characterised by a combination of clinical, biochemical and radiological features as shown in Table 2-1 (Donn et al., 2017b). The features listed in Table 2-1 may also be seen in other conditions such as sepsis, congenital pneumonia and hypothermia (Hamvas, 2011). In practice, the smallest and most preterm infants may not show many of those features. This may be because they have received mechanical ventilation and exogenous surfactant replacement shortly after birth that may conceal the classical features of RDS

An important feature of RDS is the timing of onset. It occurs within the first few hours after birth and usually peaks in severity at 48 to 72 hours of age (Hamvas, 2011). RDS can be fatal but most infants start to recover by 72 hours

of age. Therefore, respiratory signs in an infant that first occur after the first 48 hours of life are likely to be due to other underlying pathologies.

Clinical signs	Radiological features	Biochemical analysis
Tachypnoea	Diffuse reticulogranular pattern ('groundglass' appearance) of lung fields	Respiratory acidosis
Grunting	Bilateral, homogenous opacification	
Nasal flaring	Air bronchograms	
Increased use of accessory muscles	Indistinct outlines of diaphragm and cardiac borders	
Cyanosis		
Reduced oxygen saturations		
Apnoea		

Table 2-1 Clinical, radiological and biochemical features of RDS

RDS can affect infants of all gestational ages but is more common in preterm infants (Hamvas, 2011). The more preterm an infant is the more likely he or she is to have a diagnosis of RDS (Donn et al., 2017b). As described above, extremely preterm infants often do not have many clinical or radiological signs due to the use of surfactant. Therefore they do not necessarily display the typical features of RDS and are sometimes referred to as having 'respiratory insufficiency of the newborn' (Greenough et al., 2008; Hamvas, 2011).

2.4 Ventilator-associated lung injury (VALI)

Lung injury related to mechanical ventilation is often referred to as 'ventilator-induced lung injury' (VILI). However, the medium-term clinical manifestation of lung injury related to mechanical ventilation in human infants is bronchopulmonary dysplasia (BPD). As shown in Figure 2-1 the causes of BPD are complex and multifactorial in nature (Attar et al., 2002). Therefore, the term 'ventilator-associated lung injury' (VALI) is now increasingly used (Jarreau, 2015) when referring to human infants. VILI is used in relation to lung injury in animal models caused by mechanical ventilation (Rimensberger, 2015).

There are several reported mechanisms of lung injury in newborn infants (Parker et al., 1993; Jarreau, 2015). As described below, these mechanisms are categorised according to different components of ventilation (pressure, volume etc). However, like the components of mechanical ventilation, the mechanisms are inter-linked. Parker et al. (Parker et al., 1993) summarised these mechanisms in detail, describing the injurious effects of high peak airway pressures and large tidal volumes on the pulmonary endothelium and epithelium, interstitium and vasculature.

2.4.1 Barotrauma

Barotrauma results from excessive pressure delivery leading to macroscopic air leaks and microscopic alveolar damage. As summarised by Parker et al. (Parker et al., 1993), animal models have shown disruption of the endothelial barrier when high inspiratory pressures are used. This causes increased permeability of the microvascular barrier between the alveoli and the pulmonary vessels leading to leakage of fluid and protein into the airways. This leads to pulmonary oedema and reduced lung compliance. Clinically, macroscopic air leaks manifest as pulmonary interstitial emphysema (PIE), pneumothorax, pneumomediastinum, pneumopericardium and pneumoperitoneum (Parker et al., 1993).

The pulmonary oedema and structural damage seen in animal models (Dreyfuss et al., 1992) ventilated with high airway pressures were originally thought to be the main cause of VALI (Dreyfuss et al., 1992). However, subsequent work has shown that the majority of VALI is probably due to excessive tidal volumes (Hernandez et al. 1989; Parker et al., 1993).

2.4.2 Volutrauma

Volutrauma is the result of excessive inspiratory volume delivery to the alveoli. This has a shearing effect causing disruption of the alveolar type I cells (which line the alveoli and are responsible for gas exchange) and the epithelial and endothelial layers. Disruption of these cell layers leads to leakage of proteins and fluid from the capillaries into the alveoli (Wada et al., 1997; Jarreau, 2015). In animal models this can lead to low lung compliance, impaired gas exchange, reduced ventilator efficacy and reduced response to surfactant (Bjorkland et

al., 1997). Pulmonary oedema and the production of pro-inflammatory cytokines can arise, contributing to the arrest of alveolarisation (Jobe, 1999). Other aspects of alveolarisation, such as epithelial cell proliferation, elastin remodeling and angiogenesis, are also affected by excessive stretch of the alveoli due to overdistention during ventilation (Alvira et al., 2017). The compliant chest wall of preterm infants increases the risk of VALI as it enables the lungs to expand further for any given pressure than the lungs of older children or adults.

Hernandez et al. (Hernandez et al., 1989) compared varying degrees of peak inspiratory pressure (PIP) - 15, 30 and 45 cmH₂O - on three different groups of rabbit models. In the first group, the isolated lungs alone were ventilated. In the second group, rabbits were ventilated with intact chest walls that were allowed to expand normally during inflation. In the third, rabbits were placed in thoraco-abdominal casts in order to prevent expansion of the chest wall during ventilation. The casts prevented an increase in tidal volumes during lung inflation despite the use of increasing PIPs. They found that the isolated lungs showed the greatest evidence of VILI even at the lowest PIP level (15 cmH₂O). The lungs of rabbits with intact chests showed significant evidence of damage when ventilated at 30 and 45 cmH₂O. However, the lungs of rabbits with tidal volumes restricted by the thoraco-abdominal casts showed no evidence of lung injury, even at the highest PIP levels. Similar results were seen in other animal studies (Parker et al., 1993) in which greater alveolar epithelial damage was caused by large tidal volumes than by high airway pressures (Parker et al., 1993). These results support the argument that it is the 'stretch' caused by excessive tidal volume delivery rather than delivery of excessive pressures that lead to VILI (Korones, 2011).

Bjorklund et al. (Bjorklund et al., 1997) demonstrated that even tidal volumes that are not considered excessive can cause injury to the surfactant deficient lung. They investigated the effects of positive pressure ventilation in a small group of preterm lambs immediately after birth. Pairs of lambs were investigated. One from each pair was randomly assigned to receive positive pressure ventilation followed by surfactant and mechanical ventilation. The other was assigned to receive just surfactant and mechanical ventilation. Importantly, the volumes of gas administered to the lambs that received positive pressure ventilation were less than the potential lung volumes of those lambs.

The authors found clinical evidence of lung injury and more persistent respiratory failure in the lambs that received positive pressure ventilation compared to those that did not. The extent of lung injury seen in histology specimens was also greater in the lambs that received positive pressure ventilation. These results remain important today in considering how to limit volutrauma in the delivery room immediately after birth in an infant who is likely to be surfactant deficient.

Excessive alveolar stretch due to mechanical ventilation may also lead to altered expression of genes related to normal pulmonary development (Jarreau, 2015). This excessive stretch disrupts the normal generation of elastin and extracellular matrix proteins leading to abnormal septation of alveoli and abnormal microvasculature (Jarreau, 2015).

Therefore the evidence supporting volutrauma as a prime mediator of lung injury also indicates that, once injury has occurred, it may not be possible to reverse. In addition, it may be perpetuated by alterations in physiological and genetic pathways.

2.4.3 Atelectotrauma

Atelectotrauma describes lung injury caused when alveoli repeatedly collapse and re-open (Pinhu et al., 2003). Alveolar collapse is caused by loss of functional residual capacity and under-expansion of the alveoli with inadequate tidal volume delivery (Attar et al., 2002; Jobe, 1999). The alveoli are re-opened, either by the tractional forces exerted by adjacent open alveoli, or by further ventilation (Pinhu et al., 2003). Re-opening collapsed alveoli can cause a shearing effect that damages the alveolar lining (Pinhu et al., 2003). It can also lead to pulmonary oedema and inflammation (Jobe, 1999).

The preterm neonatal lung has very small tidal volumes and is usually surfactant deficient. Although the clinician may target an appropriate tidal volume using a ventilator this volume will not be delivered to closed lung units and therefore may lead to the overexpansion of other lung units (causing volutrauma) (Attar et al., 2002). As a result, unequal ventilation of alveoli promotes atelectotrauma and volutrauma simultaneously (Jobe et al., 1999).

2.4.4 Biotrauma

Biotrauma is the result of exposure of preterm lungs to inflammatory mediators. These are generated in the context of in-utero or postnatal infection (Donn et al., 2011), mechanical ventilation (Attar et al., 2002) or reactive oxygen species (Alvira et al., 2017). In-utero exposure to inflammatory mediators may also disrupt development of the fetal lung (Alvira et al., 2017). Therefore, a preterm infant's lung may be susceptible to biotrauma even before birth. Postnatal infection is also an independent risk factor for BPD (Alvira et al., 2017).

High inflation pressures and large tidal volumes lead to increases in inflammatory cytokines in animal models (Tremblay et al., 1997) and ventilated adult humans (Ranieri et al., 1999). In a study of adults with acute RDS, Ranieri et al. (Ranieri et al., 1999) found increased concentrations of inflammatory mediators in blood and bronchoalveolar lavage samples in patients randomised to ventilation with larger tidal volumes. Preterm infants have different pulmonary structure and different underlying pathologies to adults requiring ventilation. However, similar findings have been noted in neonatal populations (Speer 2003 and 2009).

Lung injury may also cause dissemination of inflammatory markers to other organs. Animal studies have shown that cytokines and bacteria from injured lungs translocate into the systemic circulation. This leads to the involvement of other organs in the inflammatory response. (Pinhu et al., 2003).

Therefore, mechanical ventilation can either precipitate or potentiate biotrauma in preterm infants who are already predisposed to VALI.

2.5 Management options to limit VALI

2.5.1 Antenatal administration of maternal glucocorticoids

Antenatal glucocorticoids administered to a pregnant woman have a number of effects on the fetal lung. They improve lung maturity by accelerating the development of the alveolar wall lining (Jobe, 2011), thereby improving gas diffusion potential. They increase lung gas volume and surfactant production (Jobe, 2006), and work synergistically with exogenous surfactant to improve lung volumes (Jobe, 2006).

Administration of antenatal glucocorticoids to women at risk of preterm delivery between 24+0 and 34+6 weeks' gestation is now a standard of care in the United Kingdom (Roberts, 2010). The decision to use antenatal glucocorticoids in women who may deliver at 23+0 - 23+6 weeks' gestation is one made jointly by these women and senior clinicians (Roberts, 2010). A recent Cochrane review described a meta-analysis of 30 studies including 8158 infants (Roberts et al., 2017) which showed that administration of antenatal maternal glucocorticoids was associated with several positive neonatal outcomes. These included a reduction in RDS (risk ratio 0.66, 95% confidence interval 0.56 – 0.77, 7764 infants) and a reduction in the outcome of “moderate to severe RDS” (risk ratio 0.59, 95% confidence interval 0.38 – 0.91, 1686 infants). The reduction in RDS was seen if glucocorticoids were given up to seven days before delivery. No significant improvement was seen for chronic lung disease.

2.5.2 Supplemental oxygen therapy

Hyperoxia can have deleterious effects on the preterm lung and on mortality and morbidity in infants born prematurely. Hyperoxia leads to the development of free radicals and contributes to oxygen toxicity (Parker et al., 1993; Alvira et al., 2017). In animal models, hyperoxia has been shown to contribute to the process of arrested alveolarisation (Alvira et al., 2017) and inflammation (Jarreau, 2015).

2.5.3 Non-invasive respiratory support

The use of non-invasive ventilation (NIV) for infants born prematurely has increased dramatically in recent years (Schmalisch et al., 2015). As a result, fewer infants are now ventilated although reports vary as to whether this has had a positive impact on the rates of bronchopulmonary dysplasia (BPD) (Schmölzer et al., 2013). There are several different types of NIV, including nasal continuous positive airway pressure (CPAP), humidified high flow nasal cannulae (HHFNC), and nasal intermittent positive pressure ventilation (NIPPV) (Kugelman, 2015). NIV aims to provide a constant distending pressure throughout the respiratory cycle. This maintains functional residual capacity, prevents atelectasis at the end of expiration and prevents the shearing damage to the alveolar epithelium during inspiration (Parker et al., 1993). It has the potential to stent the upper airways open (Davis et al., 2009). Judicious use of

NIV, accompanied by close monitoring and supportive care, in a preterm infant can avoid the need for mechanical ventilation. European Consensus Guidelines on the management of RDS suggest using CPAP from birth if possible (Sweet et al., 2017). However the authors indicate that a fractional inspired concentration of oxygen (FiO_2) $>0.3 - 0.4$ should warrant consideration of escalation of respiratory support through administration of surfactant.

2.5.4 Surfactant

Endogenous surfactant is produced by type II pneumocytes. It acts to reduce the surface tension of the alveoli, thus limiting or preventing atelectasis (Parker et al., 1993). Type II pneumocytes may not be present, or may only be present in very small numbers, in extremely preterm infants born at <28 weeks' gestation (Parker et al., 1993). The number of functional type II pneumocytes present at birth should increase as gestational age at birth increases. However, even late preterm infants may not produce sufficient surfactant to prevent RDS (Donn et al., 2017b). In addition to being produced in adequate quantity, surfactant must also be adequately active. Factors such as infection, meconium aspiration, perinatal hypoxic events and structural lung abnormalities can all lead to deactivation of any surfactant that is produced (Kumar, 2015).

Administration of exogenous surfactant to infants with suspected surfactant deficiency or inactivation has been a standard of care for many years (Sweet et al., 2017). The aim is to reduce VALI by limiting atelectasis. However, alveolar epithelial disruption and leakage of proteins into the airways can inactivate or reduce surfactant production. Pulmonary repair mechanisms, including the formation of fibrin, can reduce the function and distribution of surfactant (Parker et al., 1993).

Therefore exogenous surfactant given in the early stages of RDS reduces VALI in the form of air leaks and BPD (Bahadue et al., 2012). However, surfactant deficiency or inactivation may persist in some infants due to ongoing lung injury.

2.5.5 Caffeine therapy

Caffeine citrate is now considered standard therapy for preterm infants requiring respiratory support (Sweet et al., 2017). Whilst its primary role is in prevention of apnoea of prematurity it is also associated with other outcomes. These

include a reduction in unsuccessful extubation (Henderson-Smart et al., 2010), reduced rates of BPD, and earlier cessation of mechanical ventilation, NIV and supplemental oxygen (Schmidt et al., 2006). It is also associated with reduced rates of death or adverse neurodevelopmental outcomes at 18 to 21 months (Schmidt et al., 2007). Therefore, it has a role as an adjunctive treatment in limiting the impact of VALI and the long-term effects of VALI.

2.5.6 Postnatal corticosteroid administration

Corticosteroids reduce pulmonary inflammation and therefore would appear to be useful adjuncts in reducing VALI. There has been much research and changes in practice regarding corticosteroid administration over the years. A recently published Cochrane review indicated that the benefits of early systemic corticosteroids, given within the first eight days of life, did not outweigh the adverse side effects (Doyle et al., 2017a). However, a review of systemic corticosteroids given after seven days of life did show a reduction in unsuccessful extubation and in BPD at 36 weeks' corrected gestational age (Doyle et al., 2017b). Therefore, systemic corticosteroids appear to limit VALI to some extent but the long-term outcomes are not established. They are also associated with important side effects such as growth restriction and metabolic effects (Doyle et al., 2017b). Inhaled corticosteroids (Shah et al., 2017) and low-dose systemic corticosteroids (Yates et al., 2016) are now a focus of research.

2.5.7 Mechanical ventilation via an endotracheal tube

Despite the increase in the use of NIV, mechanical ventilation via an endotracheal tube (ETT) remains the mainstay of treatment for infants for whom NIV is not adequate. Although some centres aim to use NIV for all spontaneously breathing infants, regardless of their gestational age at birth, many centres continue to use mechanical ventilation for infants born at the extremes of prematurity (Sinha et al., 2011). Therefore, mechanical ventilation remains a fundamental treatment strategy for the management of infants with respiratory failure.

2.6 Modern ventilator techniques

2.6.1 Synchronisation

Synchronisation is now a common aspect of neonatal ventilation. Ventilator algorithms aim to synchronise delivery of the ventilator's positive pressure inflation with the infant's spontaneous respiratory effort. This is referred to as patient-triggered ventilation (Sinha et al., 2011). Synchronisation can be achieved using a pneumotachograph or a hot wire anemometer to detect signals from the infant indicating the start of spontaneous inspiration (Donn et al., 2015). These signals are usually changes in airway pressure or flow rate. They then 'trigger' the ventilator to deliver an inflation (Donn, 2009). Synchronisation is associated with a reduction in the incidence of pneumothorax and a reduction in duration of ventilation. However the efficacy of synchronisation is rarely reported in published trials (Greenough et al., 2016).

2.7 Types of mechanical ventilation

There are many different strategies to deliver mechanical ventilation via an endotracheal tube. They are split into two groups, tidal ventilation and high frequency ventilation (Donn, 2009). Tidal ventilation encompasses many types of ventilation. These modes aim to mimic physiological negative pressure respiration by delivering positive inspired inflations and enabling passive expiration using the lung's elastic recoil. High frequency ventilation delivers smaller gas volumes at very high rates using relatively high constant distending airway pressures.

2.7.1 Tidal ventilation

The different types of tidal ventilation can be classified according to the control variable that is targeted by the clinician (Sinha et al., 2008). These variables consist of pressure, volume and flow. In practice, volume is the integral of flow (Sinha et al., 2008) and these two variables are controlled together. Control of volume and flow forms the basis of volume-controlled ventilation (VCV) that will be discussed in more detail in Section 2.10.1. Therefore conventional ventilation is delivered using either volume or pressure as the target variable.

Tidal ventilation can subsequently be sub-divided into modalities according to the variables that trigger, limit or end the inflation. These variables are known as phase variables (Donn et al., 2015). Pressure, volume, flow and time can all be used as phase variables (Sinha et al., 2008).

Control and phase variables are combined to deliver inflations comprise the mode of ventilation. Modes include:

- intermittent mandatory ventilation (IMV),
- synchronised intermittent mandatory ventilation (SIMV),
- assist/control ventilation (A/C),
- pressure support ventilation (PSV).

Table 2-2 summarises the way control and phase variables that can be applied to different modes.

Mode	Control variables	Phase variables
Intermittent mandatory ventilation	Pressure	Time, pressure, flow
Synchronised intermittent mandatory ventilation	Pressure or volume/flow	Time, pressure, flow
Assist/control ventilation	Pressure or volume/flow	Time, pressure, flow
Pressure support ventilation	Pressure	Flow

Table 2-2 Control and phase variables for different ventilator modes

2.7.2 High frequency oscillatory ventilation

High frequency ventilation facilitates gas exchange in a very different way compared with tidal ventilation. There are several types of high frequency ventilation although, in the context of this thesis, only one will be discussed here. High frequency oscillatory ventilation (HFOV) uses a mean airway pressure higher than that which would be generated using equivalent tidal ventilation. It combines this with very small tidal volumes delivered at a very fast rate. The tidal volumes may be less than the anatomical dead space. Within a HFO ventilator a diaphragm is used to oscillate a bias flow of gas that creates both an active expiration phase as well as an active inspiration phase (Bollen et al., 2015).

2.8 Types of tidal ventilation

2.8.1 Intermittent mandatory ventilation

In this mode, the clinician sets the desired PIP (control variable), PEEP, inspiratory time (phase variable) and mandatory rate (the number of inflations delivered per minute). The infant can breathe spontaneously but breathing is not synchronised with delivered inflations during inspiration or expiration. If spontaneous breathing is faster than the mandatory rate, or asynchronous with the ventilator, those breaths will only be supported by PEEP (Donn et al., 2015). In this mode, the volume of gas reaching the infant is not controlled by the ventilator and will vary according to the PIP and the infant's lung compliance.

2.8.2 Synchronised intermittent mandatory ventilation

This mode synchronises delivered inflations with the infant's spontaneous respirations. It can be used with either pressure or volume as the control variable. If pressure is the control variable, the clinician sets the desired PIP (the control variable), the PEEP, the inspiratory time (phase variable) and the mandatory rate. The ventilator aims to synchronise all inflations per minute with the infant's spontaneous breaths. If the infant's spontaneous respiratory rate is higher than the mandatory rate, the extra breaths will only be supported with PEEP. As with IMV, the volume of inspired gas is not controlled by either the ventilator or the clinician (Donn et al., 2015).

2.8.3 Assist/control ventilation

In assist/control (A/C) ventilation, every spontaneous breath that reaches the trigger threshold is supported by a delivered inflation from the ventilator. Therefore, all of the infant's spontaneous respirations will be supported unlike the SIMV mode that only supports the mandatory rate. The control variables for A/C ventilation can be either pressure or volume (combined with flow). In pressure assist/control ventilation (PCV), the clinician selects the desired PIP (control variable) as well as the PEEP, inspiratory time and mandatory rate. The volume of gas reaching the infant is not controlled by either the infant or the clinician (Sinha et al., 2011). In volume assist/control ventilation (VCV), the control variables are volume and flow. These are fixed at the desired level by the clinician and therefore the volume of gas reaching the infant can be directly

controlled. The clinician can also set the PEEP and the mandatory rate, but the PIP is not controlled by the clinician (Sinha et al., 2011). This will be described in more detail in Section 2.10.1.

2.8.4 Pressure support ventilation

Pressure support ventilation (PSV) can be used alone or in combination with SIMV but it requires the infant to be breathing spontaneously. In this mode spontaneous breaths that reach the trigger threshold are supported by a set inspiratory pressure. However, the duration of the inflation is limited by the flow rate. When the flow rate reaches a set proportion, the ventilator cycles into expiration. This aims to enable the ventilator to synchronise with the infant's spontaneous expiration as well as inspiration. If the infant is apnoeic, no inflations will be delivered (Donn, 2009).

2.9 Pressure-limited ventilation

Pressure-limited ventilation (PLV) encompasses several different modes, including time-cycled pressure-limited ventilation (TCPL), pressure A/C ventilation, pressure SIMV and PSV. Historically, PLV has been in use in neonatology longer than volume-targeted modes due to previous technical limitations that made volume-targeted ventilation (VTV) impractical (Sinha et al., 2011). The neonatal community has therefore had more experience of using PLV.

In PLV, the clinician targets the pressure of gas being delivered to the infant. In practical terms, this usually involves adjustment of the PIP according to the infant's condition and gas exchange. The ventilator aims to achieve the desired pressure as quickly as possible during inspiration and sustain that pressure until expiration. It does so by delivering gas using a variable flow rate, with the gas flow to the infant being fastest at the start of inspiration before slowing down towards the end of inspiration. Figure 2-2 demonstrates the pressure, flow and subsequent volume wave patterns seen on pulmonary graphics during one inflation (Sinha et al., 2011).

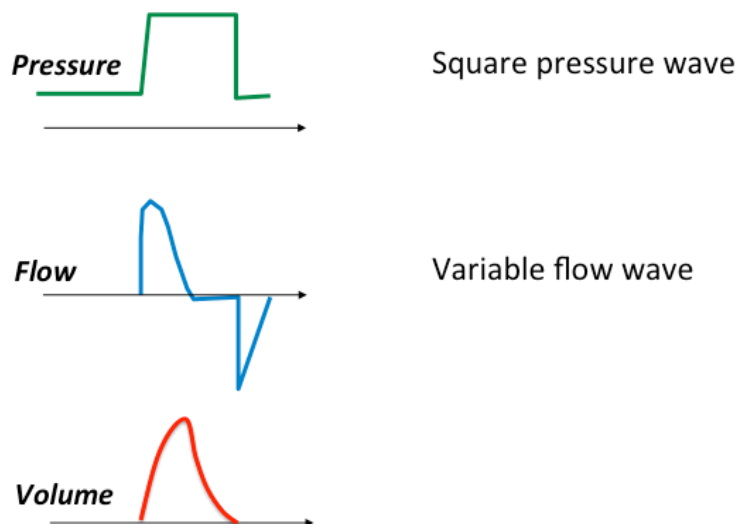


Figure 2-2 Pulmonary graphics during one inflation of PLV

During PLV the ventilator will always aim to deliver the PIP set by the clinician, regardless of the lung compliance. The volume of gas reaching the infant is not controlled. As lung compliance improves, lung expansion will be greater for any given pressure. Therefore, using PLV, the volume of gas reaching the infant's lungs will increase despite the PIP remaining unchanged. This can lead to volutrauma. Likewise, if lung compliance worsens, the volume of gas reaching the infant's lungs will decrease if the PIP remains unchanged, leading to atelectotrauma.

Since advances in technology have made the use of VTV possible over the last twenty years (Sinha et al., 1997) various modes of VTV have been introduced into neonatal units with the aim of limiting volutrauma and atelectotrauma.

2.10 Volume-targeted ventilation

Volume-targeted ventilation (VTV) modes allow the clinician to control the volume of gas delivered to the infant with the aim of limiting volutrauma and atelectotrauma. Different VTV modes control gas volumes in different ways. VCV and volume SIMV are 'pure' volume-targeted modes in that the desired volume (and flow) are set by the clinician. Other VTV modes are referred to as hybrid modes. These modes deliver pressure and gas flow in the same way as

PLV but do so in a way that targets the desired tidal volume (Sinha et al., 2011). This shall be discussed in more detail below.

2.10.1 Volume-controlled ventilation

When using volume-controlled ventilation (VCV) the primary aim is to keep the expired tidal volume within a desired range. The expired tidal volume is measured by a flow sensor situated as close to the ETT as possible. The flow sensor monitors many parameters including airway pressures, tidal volumes and gas flows to and from the ventilator and the infant.

The clinician sets the desired volume of gas that the ventilator will deliver to the infant whenever the infant inspires (or according to the pre-set mandatory respiratory rate if the infant is apnoeic). The ventilator aims to deliver this volume irrespective of the lung compliance or the peak inspiratory pressure (PIP) required to deliver it. The gas is delivered at a constant flow rate also set by the clinician. However, not all of the volume of gas that leaves the ventilator reaches the infant's lungs. Much of it remains within the circuit between the ventilator and the infant and is referred to as "compressible volume loss". Some is also lost as leak around the uncuffed ETT. The compressible volume loss increases as lung compliance decreases. The clinician intermittently adjusts the set volume manually on the ventilator to aim to deliver a volume to the infant's lungs that is within a desired range and achieves acceptable gas exchange (Donn et al., 2011; Sinha et al., 2011).

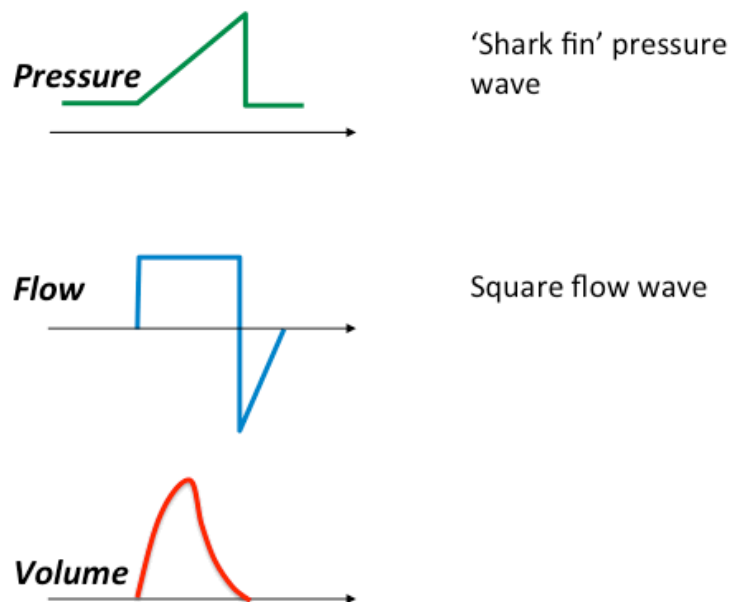


Figure 2-3 Pulmonary graphics during one inflation of VCV

When using VCV the clinician aims to ensure that the tidal volumes are kept within a desired range by adjusting the delivered volume. However it may not be practically possible to achieve specific tidal volumes with each inspiration. The volume of gas that actually reaches the infant is dependent on lung compliance, which can vary rapidly and frequently. It is also dependent on the clinician who may not make adjustments frequently enough to respond to the rapidly changing lung compliance (Sinha et al, 2011). A reduction in tidal volumes will be seen with worsening lung compliance unless the delivered volume is increased by the clinician. Excessive tidal volumes will be generated as lung compliance improves unless the clinician weans the delivered volume. Careful titration according to lung compliance and the infant's condition is required to limit the risk of volutrauma and atelectotrauma.

Regarding inspiratory pressure the ventilator will generate whatever PIP is necessary to deliver the pre-set tidal volume (although this can be limited by the clinician for safety reasons). There is, therefore, an increase or reduction in the generated PIP as lung compliance deteriorates or improves respectively. However the PIP is not specifically controlled by the ventilator (Donn et al, 2011; Sinha et al., 2011) and this may contribute to barotrauma.

2.10.2 Volume guarantee

The term 'volume guarantee' is a misnomer because, when used in combination with a PLV mode, the ventilator *aims* to deliver the desired tidal volume with every inspiration but cannot *guarantee* it (Keszler et al., 2007). VG can be used with several PLV modes, including TCPL, SIMV, PCV and PSV. For the purpose of this review, the term VG shall be used to refer one specific mode, pressure assist/control ventilation combined with VG (pressure A/C + VG). When discussing other PLV modes combined with VG, the full name shall be stated (eg. PSV+VG).

Volume guarantee is combined with pressure-limited modes to create a hybrid mode. This hybrid mode generates flow and pressure in the same way as its reference PLV mode (see Figure 2-2) whilst also aiming to control the tidal volume. It uses a servo-controlled mechanism and relies on microprocessor technology within the flow sensor to enable an automated feedback mechanism. This enables the ventilator to make specific changes to the PIP in order to target a specific tidal volume (Sinha et al., 2011).

When using this mode, the clinician sets a desired tidal volume of gas. The ventilator aims to deliver this volume by adjusting the PIP on a breath-by-breath basis. It uses the infant's expired tidal volume, measured by the flow sensor, as a reference. It then adjusts the PIP up or down to aim to deliver the desired tidal volume. Adjustments to the PIP are made in small increments to avoid large fluctuations in volume delivery (Keszler et al., 2007). The gas flow rate is variable and occurs more rapidly at the beginning of an inspired breath. This mechanism aims to overcome the problem of compressible volume loss and the breath-by-breath adjustments aim provide tighter control over the targeting of volume with each inspiration (Sinha et al., 2011) (see Figure 2-4).

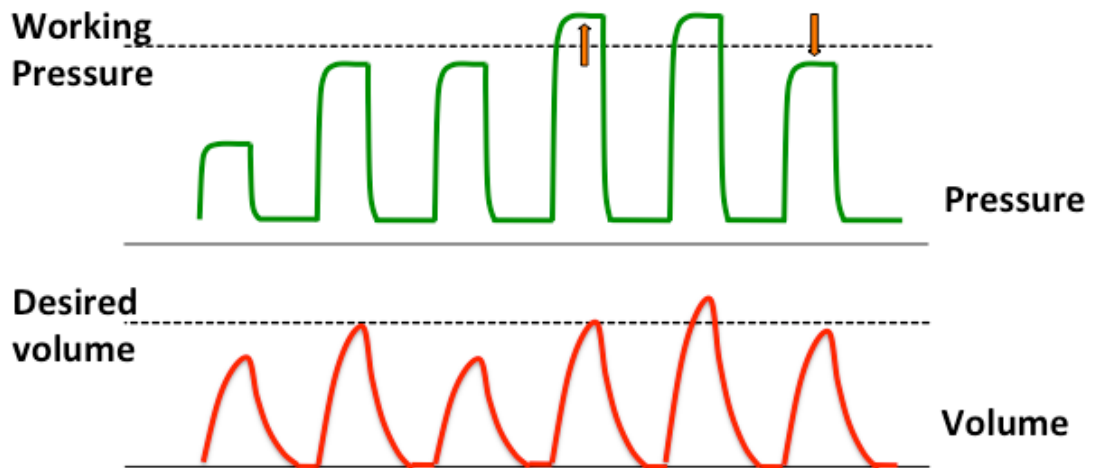


Figure 2-4 Changes in peak inspiratory pressure and tidal volume during volume guarantee ventilation. (Adapted from Keszler et al., 2007)

Figure 2-4 demonstrates the effect of automated adjustments to the PIP in order to achieve the target tidal volume during VG. During the first inspiration in Figure 2-4 the desired tidal volume is not achieved using the PIP generated during that breath. The PIP is increased during the second inspiration and the target tidal volume is achieved. The ventilator then uses the same PIP to deliver the third tidal volume but, during this inspiration, the desired tidal volume is not achieved. The ventilator therefore increases the PIP again during the next inspiration to aim to deliver the desired tidal volume. During the fifth inspiration the tidal volume delivered is greater than the desired volume. The PIP is therefore reduced during the sixth inspiration and the target tidal volume is achieved.

Another important difference between VCV and VG is the way in which gas flow differs during inspiration. In VCV, the clinician sets the flow so that gas flow is constant throughout inspiration and therefore the maximal tidal volume and PIP are reached at the end of inspiration. In VG the flow is maximal at the beginning of inspiration meaning that PIP and tidal volume are achieved earlier in inspiration. When the designated PIP has been achieved the gas flow rate decreases during the remainder of inspiration (see Figure 2-5) (Sinha et al., 2011). It is suggested that a high flow rate earlier in inspiration may be beneficial for infants with poorly compliant lungs who require high opening

pressures and therefore may offer a theoretical advantage over other forms of VTV in the acute stage of RDS (Sinha et al., 2011).

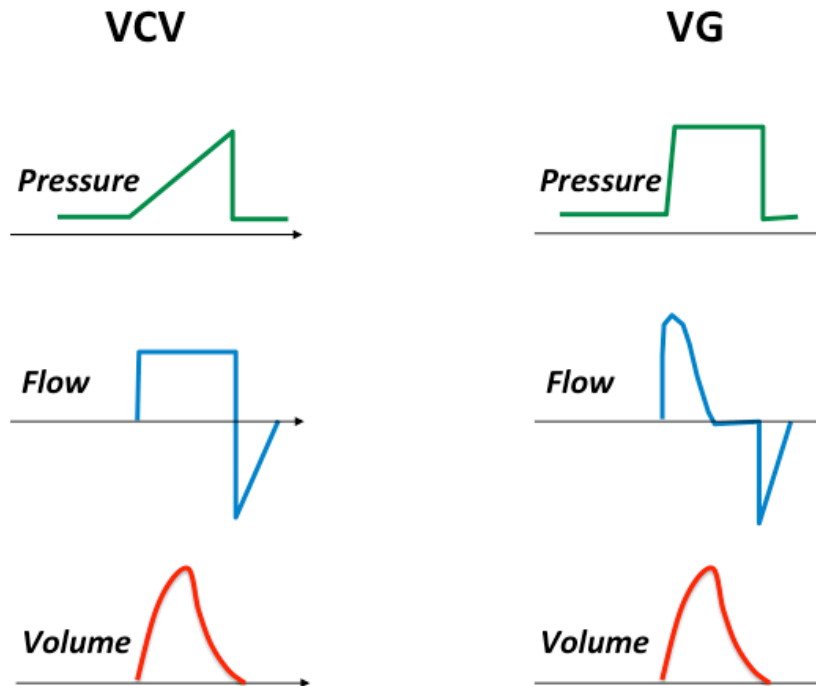


Figure 2-5 Differences in gas flow and pressure waveforms in VCV and VG

Figure 2-5 demonstrates the pressure, flow and volume waveforms seen during inspiration using both VCV and VG. In VCV, the flow is constant throughout inspiration so that pressure increases during, and is maximal at the end of, inspiration. In VG, gas flow is maximal at the start of inspiration so that the peak pressure is achieved early and is sustained throughout inspiration. As it is a hybrid mode, the waveforms seen when VG is used are the same as those seen when PLV is used.

2.10.3 Pressure-regulated volume control ventilation

Pressure-regulated volume control (PRVC) is another hybrid mode of ventilation. It is similar to VG in that the ventilator uses an automated feedback mechanism to increase PIP to achieve a preset tidal volume. It differs from VG in that PIP is adjusted based on the average PIP of the four previous breaths.

The initial breath is delivered using a PIP generated at 10cmH₂O above the positive end expiratory pressure. The ventilator then uses the infant's lung compliance to calculate the PIP required to deliver the set tidal volume. It delivers the next three breaths using PIPs at 75% of that calculated. If the target tidal volume is not achieved the ventilator increases the PIP by 3cmH₂O (Sinha et al., 2011).

2.10.4 Volume-assured Pressure Support ventilation

Volume-assured pressure support ventilation (VAPS) is a hybrid mode that combines the principles of PSV and VCV. Like PSV, it can only be used if the infant is spontaneously breathing (Sinha et al., 2011). When an inflation is triggered the ventilator delivers gas at a variable flow rate. The volume of delivered gas is measured when the flow has decelerated to a specific level. If the desired volume has been achieved the ventilator cycles into expiration, similar to PSV. If the desired volume has not been achieved the ventilator continues the inflation but uses the principles of VCV. In this way, inspiratory flow is continued at a constant rate and the inspiratory time is increased until the desired volume has been achieved. The PIP may also be increased to ensure that the desired volume is reached. The pulmonary graphic waveforms look similar to those seen in VCV at this point, with a partially or completely square flow waveform and a 'shark fin' pressure waveform (Sinha et al., 2011).

2.11 Other modes of VTV

Other hybrid modes of VTV include volume support ventilation and pressure augmentation. Volume support ventilation combines elements of PSV and PRVC. It relies on spontaneous breathing and, like PSV, is flow-cycled. As with PRVC, the PIP is adjusted with every breath to aim to achieve the target tidal volume (Sinha et al., 2011). Pressure augmentation also requires spontaneous breathing. It aims to achieve a minimal tidal volume by adjusting inspiratory flow during inspiration (Sinha et al., 2011).

2.12 Review of the literature on the use of VTV in newborn infants

Much of the evidence for the use of volume-targeted ventilation (VTV) comes from clinical trials with short-term primary outcome measures. Such outcome measures include

- ventilatory or physiological parameters (Abubakar et al, 2001; Cheema et al., 2001; Herrera et al., 2002; Olsen et al., 2002; Keszler et al., 2004; Lista et al., 2004; Abubakar et al., 2005; Lista et al., 2006; Nafday et al., 2005; Hummler et al., 2006; Polimeni et al., 2006; Cheema et al., 2007; Scopesi et al., 2007; Swamy et al., 2008),
- clinical outcomes before discharge from hospital (Piotrowski et al., 1997; Sinha et al., 1997; D'Angio et al., 2005; Singh et al., 2006; Duman et al., 2012; Guven et al., 2013).

Only two clinical trials have reported medium-term respiratory and neurological outcomes (Singh et al, 2009; Stefanescu et al., 2015). Many of the early studies were small feasibility studies and subsequent trials used small sample sizes. However, despite their modest sizes, these studies provide useful data on the safety and efficacy of VTV in the clinical setting.

2.12.1 Using VCV to target tidal volumes

Sinha et al. (Sinha et al., 1997) published a randomised controlled trial comparing TCPL ventilation with VCV. This was the first study to investigate the safety and efficacy of VCV using fixed inspiratory flow in preterm infants. Fifty preterm infants with a birth weight >1500g and a diagnosis of RDS requiring mechanical ventilation were enrolled. All infants received surfactant but less than half were exposed to antenatal glucocorticoids. The target tidal volume in both groups was 5-8 mls/kg. Therefore the only difference between groups was the mode of ventilation. The authors defined 'success' criteria (alveolar-arterial oxygen gradient of <13 kPa or a mean airway pressure of <8 cmH₂O for at least 12 hours, or until extubation if this occurred sooner) to standardise the primary outcome measure.

By targeting tidal volumes using VCV, infants achieved the 'success' criteria significantly faster compared with those in the TCPL group (65.5 hours versus 125.8 hours respectively, $p < 0.001$). The strengths of the study included the use of a strict protocol, objective criteria to measure the primary outcome and the use of the same ventilator in both groups, thereby eliminating device-related differences. One limitation is the small sample size that is acknowledged by the authors in relation to interpretation of the findings that BPD and major abnormalities on cranial ultrasound scan were less frequent in the VCV group.

This was a small single centre study, limiting the generalisability of the results. However, this study was designed to assess the safety and efficacy of VCV in preterm infants and it was the first study to do so. Therefore, although it does not provide definitive results, the study achieved its purpose of demonstrating safety and efficacy.

The study was subsequently repeated by Singh et al. (Singh et al., 2006) in a two-centre study to test the safety and efficacy of VCV in smaller and more preterm infants. The same study protocol was used. There was no significant difference between the two groups in the time taken to achieve the success criteria. A post hoc analysis of infants weighing <1000g showed that infants in the VCV group met the 'success' criteria significantly faster than infants in the TCPL group (21 hours versus 58 hours respectively, $p=0.03$). Again, this study achieved its aims of assessing whether VCV was safe and efficacious in extremely small and preterm infants but its very small sample size means that it does not provide definitive results.

Swamy et al. (Swamy et al., 2008) reviewed the respiratory parameters documented hourly during the first 72 hours of ventilation (or until extubation if that occurred sooner) in 86 of the infants enrolled into the study by Singh et al. (Singh et al., 2006). They reported that expired tidal volumes were significantly less variable in the VCV group compared with the TCPL group (mean (SD) 0.871 (0.25) mls/kg versus 1.121 (0.56) mls/kg respectively, $p=0.009$). This was achieved using significantly higher PIPs (VCV mean (SD) 16.953 (3.79) cmH₂O versus TCPL 15.319 (3.12) cmH₂O, $p=0.03$) that were also more variable (VCV mean (SD) variability of 3.28 (1.38) cmH₂O versus TCPL 2.66cm (1.22) H₂O, $p=0.032$).

These data were taken from a prospective randomised controlled trial by Singh et al. (Singh et al., 2006). Therefore comparison groups were subject to a prospectively planned trial protocol and the data used by Swamy et al. (Swamy et al. 2008) were recorded prospectively. However this study was limited in several ways. It was retrospective in nature which introduces measurement bias. The validity of data recorded manually once every hour was not explored meaning that the results and conclusions are not validated. Not all infants had complete datasets for analysis, meaning that data from some infants from the

trial by Singh et al. (Singh et al. 2006) were not included in this study. This limits the reliability of the data published by Swamy et al. (Swamy et al. 2008)

In summary, VCV using fixed inspiratory flow may target tidal volumes more effectively using higher but more variable PIPs to achieve faster weaning of ventilation. However, these results are not definitive. Larger trials that include greater numbers of infants and use validated means of collected data on tidal volumes and airway pressures would provide more reliable data.

2.12.2 Using VG to target tidal volumes

VG is the most commonly studied mode of VTV in clinical trials of neonatal ventilation. The feasibility and effects of combining VG with pressure-limited modes in preterm infants were demonstrated in small crossover studies or randomised controlled trials looking at short-term end points such as ventilator parameters and their variability (Cheema et al., 2001; Abubakar et al., 2001; Herrera et al., 2002; Olsen et al., 2002; Keszler et al., 2004; Abubakar et al., 2005; Nafday et al., 2005; Scopesi et al., 2007) and short-term clinical outcomes (Cheema et al., 2007; Duman et al., 2012; Guven et al., 2013).

2.12.3 The effect of VG on tidal volumes

Most of these studies showed that mean tidal volumes were similar when VG was used to target tidal volumes compared with a pressure-limited mode (Cheema et al., 2001; Abubakar et al., 2001; Keszler et al., 2004; Abubakar et al., 2005; Scopesi et al., 2007) although in one study (Herrera et al., 2002) mean tidal volumes were lower in the VG groups compared with SIMV. However, tidal volumes were less variable in VG modes compared with pressure-limited modes, often reaching significance (Abubakar et al., 2001; Keszler et al., 2004; Scopesi et al., 2007). Herrera et al. (Herrera et al., 2002) demonstrated that the proportion of tidal volumes exceeding 7mls/kg was significantly lower when SIMV+VG was used at tidal volumes of 4.5mls/kg and 3.0mls/kg compared with SIMV alone.

The data from the studies above refer to the first few hours or days after birth. Traditionally, a target tidal range of 4-6mls/kg has been used for ventilated preterm infants (Van Kaam et al., 2015). However there is some evidence to suggest that targeting tidal volumes >6mls/kg may be more appropriate for

infants who are ventilated for more than a few days. Keszler et al. (Keszler et al., 2009) undertook a retrospective review of the tidal volumes generated over the course of three weeks in extremely low birth weight (ELBW) infants (birth weight <800g) who were receiving pressure A/C+VG or PSV+VG. Reported practice in the unit was to allow mild permissive hypercapnia after the first few days of ventilation. They observed that both set and measured tidal volumes increased over time, indicating that ventilator-dependent ELBW infants may require higher tidal volumes over time to achieve a target ventilation strategy. The study is limited, however, by its retrospective nature and exclusion of both larger preterm infants and other infants who were switched to other ventilatory modalities.

Hunt et al. (Hunt et al., 2018) reported similar findings in a small crossover study of 18 infants born at <32 weeks' gestation and ventilated for at least a week. They found that the infants' mean expired tidal volumes were greater prior to the introduction of VTV than when a target tidal volume of 4mls/kg was used in conjunction with VTV. They also found that the infants' work of breathing was reduced when a tidal volume of 7mls/kg was used instead of 4-6mls/kg. The strengths of this study include its prospective, randomised design and use of an objective measure of work of breathing (transdiaphragmatic pressure-time product, PTPdi). However, the study is small and undertaken in one centre which limits its generalisability. Two infants received SIMV whereas 16 received A/C ventilation. The use of SIMV may have impacted on those two infants' work of breathing as not all breaths are supported with SIMV. The authors do not state which mode of VTV was used.

Whilst the studies by Keszler et al. (Keszler, 2009) and Hunt et al., (Hunt et al., 2018) have several methodological limitations they do highlight an area for further research. Whilst many infants are extubated within a few days, some require longer periods of ventilation and a higher target tidal volume range may be more suitable for these infants.

2.12.4 The effect of VG on airway pressures

Two crossover studies reported that PIP was lower when VG was compared to pressure-limited modes without VG (Cheema et al., 2001; Scopesi et al., 2007). When comparing two VG modes, Abubakar et al. (Abubakar et al., 2005) found

that PIP was significantly lower when VG was combined with pressure assist-control (A/C) compared with SIMV+VG. However, this difference was only found when ventilator-supported breaths were analysed. Not surprisingly, when lower tidal volumes are targeted, mean PIP is lower (Herrera et al., 2002).

The crossover studies demonstrated that VG is safe and effective in newborn infants but many are limited by methodological factors such as inclusion bias, short duration of study periods and lack of randomisation. In one study (Cheema et al., 2001), the results should be interpreted with particular caution because the maximum PIP limit, a safety limit set by the clinician to prevent the ventilator generating pressures higher than that limit, was not adjusted during the study. This will have prevented the ventilator from increasing the PIP beyond this limit if required to achieve the set tidal volumes. In turn, this may have affected the reported PIP and tidal volumes values.

2.12.5 Evidence for other modes of VTV

Markstrom et al. (Markstrom et al., 1996) studied 13 surfactant-depleted piglets and found that the decelerating inspiratory flow pattern in PRVC led to increased carbon dioxide removal (and therefore presumed better alveolar ventilation) than the constant flow pattern of VCV. There are no studies in human infants to corroborate this. In two studies (Piotrowski et al., 1997; D'Angio et al., 2005) PRVC ventilation was used as the volume-targeted mode but was compared with a PLV mode. Piotrowski's study (Piotrowski et al., 1997) of PRVC is reviewed below in section 2.12.7. D'Angio et al. (D'Angio et al., 2005) claim that the same minute ventilation is achieved using lower VT and lower PIP in the PRVC group compared to the SIMV group. However, the quoted VT values are inspiratory and measured at the ventilator, therefore not taking account of ETT leak and compressible volume loss.

2.12.6 Maintaining partial pressure of carbon dioxide

There is a recognised link between hypocarbia and severe intracranial pathologies (Fujimoto et al., 1994; Okumura et al., 2001). Therefore it is imperative to prevent hypocarbia when ventilating preterm infants using VTV. Many studies report blood gas results as a measure of gas exchange, either from arterial or capillary samples or from transcutaneous recordings. Some

found no difference when VG is compared to pressure-limited modes (Herrera et al., 2002; Cheema et al., 2007; Scopesi et al., 2007). Keszler et al. (Keszler et al., 2004) found that the partial pressure of carbon dioxide (PaCO_2) was below the target range on fewer occasions when VG was used to target tidal volumes (20.1% pressure A/C+VG versus 36.3% pressure A/C, $p<0.001$) although there was no difference in the proportion of episodes above the target range.

A retrospective cohort study reported that, in the 38 preterm infants who received SIMV+VG for 48 hours after admission, 92% of PaCO_2 values were between the pre-specified range of 25 and 65 mmHg (3.3 - 8.7kPa) (Dawson et al., 2005). The mean target tidal volume was 3.98mls/kg and ranged from 3.5-5.1mls/kg. However, this study is limited by its retrospective design and lack of comparison group.

In a prospective randomised controlled trial in which SIPPV was compared with SIPPV+VG in 40 preterm infants with RDS, fewer episodes of hypocarbia were reported in the SIPPV+VG group (32%) than in the SIPPV group (57%) (Cheema et al., 2007). The difference did not reach statistical significance, possibly due to the small sample size. Infants born at >25 weeks' gestation had significantly fewer episodes of hypocarbia, defined as $\text{PaCO}_2 < 5\text{kPa}$, when SIPPV+VG was used compared with SIPPV (27% versus 61% respectively, $p=0.048$). All PaCO_2 values were outside the normal range in the SIPPV+VG group in infants born at 23-25 weeks' gestation. However, this was a post-hoc stratification of data analysis and only seven infants in total were born at <25 weeks' gestation, limiting the reliability and applicability of this result.

2.12.7 Duration of ventilation

The term 'duration of ventilation' may apply to the total duration of mechanical ventilation via an ETT or it may apply to the first period of ventilation only. Clinicians may have differing opinions as to when an infant is ready for extubation. This can impose substantial bias unless this outcome is clearly defined in a study protocol.

Piotrowski et al. (Piotrowski et al., 1997) described clear clinical criteria ($\text{FiO}_2 < 0.25$, PIP <12 cmH₂O and a set rate of <12 breaths per minute followed by a 30-60 minute trial of endotracheal CPAP) in order to standardise the timing of

extubation. They did not find a significant difference in the time to extubation in infants ventilated with TCPL compared with infants ventilated with PRVC (median time to extubation was eight days in both groups). They did demonstrate a significantly shorter time to extubation in the PRVC group in infants weighing <1000g (11 days, 95% CI 3-19 days, in the PRVC group versus 32 days, 95% confidence interval 3-61 days, in the TCPL group, $p=0.025$). However this was a post-hoc analysis and the large confidence intervals (CIs) reflect the small sample size and limited validity of these data.

Sinha et al. (Sinha et al., 1997) and Singh et al. (Singh et al, 2006) used predefined 'success' criteria as a primary outcome measure, rather than the moment of extubation itself, in order to determine the speed of weaning. These consisted of maintenance of an alveolar-arterial oxygen gradient ($AaDO_2$) <13 kPa or MAP <8 cmH₂O for 12 consecutive hours. Duration of ventilation was a secondary outcome in these studies and referred to total duration of mechanical ventilation via an endotracheal tube. In the first study (Sinha et al, 1997) infants in the VCV group achieved the 'success' criteria significantly faster (mean 65.5 hours VCV versus 125.8 hours TCPL, $p<0.001$) and had a significantly shorter total duration of ventilation (VCV mean 122.4 hours versus TCPL mean 161.9 hours, $p<0.001$). In the second study (Singh et al., 2006) into which smaller and more immature infants were enrolled, there was no significant difference between the two groups in the time to reach the success criteria. A planned subgroup analysis of infants weighing <1000g at birth ($n=59$) showed that infants in the VCV group reached the 'success' criteria significantly faster than those in the TCPL group (VCV mean 21 hours, 95% CI 17-24, versus TCPL mean 58 hours, 95% CI 42-74; hazard ratio 1.83, 95% CI 1.04-3.2, $p=0.03$). The use of clearly defined 'success' criteria in these two studies ensured that objective measures of oxygenation and ventilator support were used to reflect routine clinical practice. This is a major strength of both studies. However objective measurements of spontaneous respiratory effort, which is an essential component of 'readiness for extubation', were not included.

Two more recently published trials report duration of ventilation as a primary outcome (Duman et al., 2012; Guven et al., 2013). Duman et al. (Duman et al., 2012) used extubation success at 48 hours as the primary outcome when comparing pressure A/C with pressure A/C+VG in a study of 45 infants. At 48

hours, 60% of infants in the pressure A/C+VG group had been successfully extubated compared to 40% in the pressure A/C group although this was not significant ($p=0.315$). They used pre-determined criteria ($FiO_2 <0.3$ and an expiratory time of 5 seconds having been loaded with aminophylline) but do not state how long infants were expected to sustain these end-points prior to extubation. Therefore the primary outcome may still have been open to subjective bias by the preferences of clinicians' regarding the timing of extubation.

Guven et al. (Guven et al., 2013) used duration of ventilation as a primary outcome in their randomised controlled trial comparing SIMV with SIMV+VG. They specified pre-determined criteria for extubation (ventilator rate 20/minute, loaded with aminophylline, $PaCO_2 <60$ mmHg, $FiO_2 <0.3$ and PIP <15 cmH₂O for eight hours) and found that SIMV+VG resulted in a significantly shorter duration of ventilation than SIMV (SIMV+VG mean (SD) 3.02 (6.76) days vs 6.93 (7.81) days, $p<0.001$). However the study was underpowered with only 72 infants completing the study instead of the required 90.

Therefore, duration of ventilation is an important short-term clinical outcome when evaluating the effect of VTV. It has important clinical and financial implications. However, varying definitions of duration of ventilation make evaluation of the evidence difficult. The evidence from studies that use objective criteria (Piotrowski et al., 1997; Sinha et al., 1997, Singh et al., 2006) suggest that VTV results in the need for shorter periods of ventilation, particularly in extremely low birth weight infants. Trial protocols should include objective criteria for extubation, or readiness for extubation, that are used to standardise practice when extubating trial participants.

2.12.8 Use of VTV in hypoxaemic episodes

Three studies have reported the effect of VTV on hypoxaemic episodes.

In a very small pilot study, Hummler et al. (Hummler et al., 2006) concluded that volume-controlled SIMV did not reduce the duration of hypoxemic episodes (oxygen saturations $<80\%$) in extremely preterm infants compared with pressure-controlled SIMV. In a small, crossover study Jain et al. (Jain et al., 2016) found a small reduction in the duration of hypoxemic episodes (oxygen saturations $<85\%$ for at least 20 seconds) when VG was used compared to

either SIMV+PS or pressure A/C ventilation. Although the reduction was statistically significant the clinical difference was only three seconds which limits the relevance of the results, something acknowledged by the authors.

Polimeni et al. (Polimeni et al., 2006) reported that the use of SIMV+VG did not alter the frequency of hypoxaemic episodes (oxygen saturations <88%) when compared to SIMV but did lead to a shorter mean duration of episodes in extremely preterm infants with a mean chronological age of 37.5 days if a target tidal volume of 6 mls/kg is used. The criteria for increasing supplemental oxygen were defined prior to the trial. However the adjustments to the supplemental oxygen made by the researchers were not recorded so that the effect of these adjustments cannot be accounted for.

2.12.9 Work of breathing

Patel and colleagues studied the work of breathing in ventilated preterm infants during the acute phase of RDS (Patel et al., 2010) and the recovery phase (Patel et al., 2009). They used the PTPdi, based on oesophageal and gastric pressures, as a measure of work of breathing. In both studies they found that targeting a volume of 4 mls/kg resulted in a higher mean PTPdi than those measured when volumes of 6 mls/kg were targeted (but not 5 mls/kg) and at baseline when volume-targeting was not employed.

2.12.10 Biological markers of lung injury

Lista et al. (Lista et al., 2004; Lista et al., 2006) analysed concentrations of inflammatory mediators (cytokines) in tracheal aspirates in two randomised controlled trials involving preterm infants with RDS. Cytokine concentrations were higher when PSV was compared with PSV+VG (Lista et al., 2004), indicating that breath-to-breath volume targeting may result in lower levels of lung inflammation. When target tidal volumes of 5 mls/kg were compared with 3 mls/kg using SIPPV+VG in both groups, higher concentrations of cytokines were isolated when tidal volumes of 3 mls/kg were targeted (Lista et al., 2006).

These results indicate that ventilating at low tidal volumes may cause atelectotrauma and greater lung inflammation. Lung inflammation may be a reflection of VILI and therefore achieving an optimal tidal volume using VTV may limit VILI. However these studies were both very small, with the first (Lista

et al., 2004) enrolling 53 patients and the second (Lista et al., 2006) enrolling only 30 patients. This greatly limits the generalisability and validity of these results. Investigating the levels of inflammation associated with different modes of VTV is important and these studies do provide exploratory data that are worthy of investigation in larger studies. However, the small numbers of infants randomised means that these results are not definitive.

2.12.11 Long-term clinical outcomes

Singh et al. (Singh et al., 2009) evaluated respiratory and gross neurodevelopmental outcomes at a median age of 22 months in infants ventilated with TCPL or VCV (Singh et al., 2006). Masked follow-up of 93% of surviving infants revealed that fewer children in the VCV group were using inhalers (odds ratio 0.32, 95%CI 0.1-0.9, $p=0.04$). However, the original study was not powered to assess long-term outcomes and there were so few cases of severe neurodevelopmental impairment that meaningful analysis was not possible. D'Angio et al. (D'Angio et al., 2005) reported neurodevelopmental outcome data for a proportion of infants in their trial. Although they did not find any differences in these outcomes, this study was not powered to detect differences in these outcomes.

Stefanescu et al. (Stefanescu et al., 2015) reported the results of a retrospective observational cohort study of infants with a birth weight of ≤ 1250 g. During the first epoch, infants received pressure-controlled ventilation. In the second infants received PSV+VG. The authors examined the effect of these ventilator modes on the combined outcome of severe neurodisability or death at 18 months' corrected gestational age. There were no significant differences between groups in the combined outcome. However, the design of this study limits its applicability in several aspects. PSV+VG requires the infants to be spontaneously breathing whereas pressure-control ventilation does not. This characteristic makes the groups substantially different. Outcome data on a large proportion of the infants (30%) could not be obtained. The retrospective nature of the study means that practices were not controlled by a protocol. Therefore the likelihood of bias, including selection and performance bias is high. The lack of randomisation indicates that prognostic factors in the two groups may not be balanced.

None of these studies were designed to assess long-term respiratory or neurodevelopmental outcomes as a primary outcome. Therefore, although these results may be interesting they are by no means definitive. Therefore there is a lack of long-term respiratory or neurodevelopmental outcome data regarding the use of VTV in infants. These are crucial outcomes in neonatology, particularly in trials of respiratory practice, and large prospective trials powered to assess these outcomes are needed to provide definitive data.

2.12.12 Meta-analyses of VTV

Currently, the only method of evaluating major morbidities such as death or CLD is by systematically combining results of different trials. A Cochrane review published in 2010 (Wheeler et al., 2010) and meta-analysis published in 2011 (Wheeler et al., 2011) comparing VTV with PLV combined the results from 12 and nine trials respectively. Overall, VTV was associated with reductions in the combined outcomes of death and BPD (number needed to treat = 8), the rate of pneumothoraces, duration of ventilation, hypocarbia, and the combined outcomes of periventricular leukomalacia (PVL) or grade III-IV intraventricular haemorrhage (IVH). Another meta-analysis by a different group of authors (Peng et al., 2014) published in 2014 consisted of 18 studies, some of which were excluded by the authors of the previous reviews or were published since the previous reviews. They reported similar findings but found no difference in the incidence of death.

The Cochrane review of 2010 (Wheeler et al., 2010) was recently updated and published in 2017 (Klingenberg et al., 2017). Several additional studies were included since the previous publication, most of which are discussed in this thesis. Only the study by Liu et al. (Liu et al., 2011) could not be reviewed in detail as it was published in Chinese and only the abstract was available in English. The authors of the 2017 Cochrane review reported similar findings to that of the previous Cochrane review. The evidence favouring the use of VTV compared to PLV was stronger in the more recent review and in both reviews the authors recommended that future studies compare different VTV modes and strategies.

2.12.13 Limitations of the data on use of VTV in newborn infants

The limitations of the individual studies have been discussed in the previous sections. All of them are small and many are single-centre which limits generalisability. Many only focus on short-term outcomes and none are powered to demonstrate significant differences in important long-term outcomes. The methodology used by some of the trials is likely to have introduced substantial bias. As a collection of studies, they are very heterogeneous, using different patients, different ventilators, different modes of VTV and control groups, and different outcomes. This heterogeneity impacts on the ability of the meta-analyses to provide strong data on the use of VTV in newborn infants. Therefore, this remains an area of neonatology in which robust data are lacking.

2.12.14 Conclusions

Most studies favour VTV with respect to short- and medium-term outcomes when compared with pressure-limited modes (Klingenberg et al., 2017). VTV maintains tidal volumes within a given range, often using lower airway pressures and achieving equivalent or improved carbon dioxide elimination. VTV modes appear to achieve this more effectively than pressure-limited ventilation even when tidal volumes are targeted in both modes. The relationship between these outcomes and clinical manifestations of VALI can be difficult to establish as studies are often limited by small sample sizes, lack of or suboptimal randomisation, and methodological bias. Therefore long-term outcome measures are preferable but difficult to achieve without large multi-centric studies. Recent reviews combining the results of several studies favour VTV over pressure-limited ventilation (Wheeler et al., 2010; Wheeler et al., 2011; Peng et al., 2014; Klingenberg et al., 2017) with regards to important short- and medium-term outcomes.

Now that VTV is considered a standard of care (Sweet et al., 2017), it is necessary to compare different VTV modes using prospective randomised clinical trials. Short-term outcomes such as readiness for extubation or duration of ventilation are still relevant to assess the safety and efficacy of protocols because these outcomes have important health and financial implications.

However, it is vital to define these outcomes *a priori* using objective criteria in order to avoid bias.

Published studies to date have compared VG or VCV with pressure-limited modes. However there is no published study comparing VG with VCV as a means of providing VTV in preterm infants. The aim of this trial was to compare VG with VCV using short-term clinical outcomes with preterm infants with RDS.

Chapter 3 Methods

3.1 Introduction

There are many modes of VTV available and used widely around the world (Klingenberg et al., 2011a). Two of these modes, volume controlled ventilation (VCV) and volume guarantee (VG), work in different ways as discussed in Chapter 2. VCV delivers a set volume of gas at a constant flow throughout inspiration, generating whatever PIP is needed to deliver the set volume of gas. Inspiratory pressure is maximal at the end of inspiration. The maximal pressure generated depends on lung compliance, airway and circuit resistance, and compressible volume loss. The duration of inspiration is dependent on the time taken to deliver the set volume at the set flow rate, and can vary from breath to breath.

When VG is used the volume and inspiratory times are set by the clinician. The flow rate peaks early in inspiration and then falls throughout the remainder of inspiration. Therefore the PIP is generated early in inspiration and maintained throughout inspiration. Using an automated, closed-loop feedback mechanism the ventilator varies the PIP with each breath in order to aim to deliver the volume set by the clinician.

These modes are both used widely to provide mechanical ventilation to newborn infants. However there are no published clinical trials comparing the two modes.

3.2 Ethical approvals

This randomised controlled trial (RCT) was conducted according to a protocol approved by The North-East York Ethics Committee on 3rd July 2013 (see Appendix 9.1). This protocol was also approved by South Tees Hospitals NHS Foundation Trust Research and Development Department on 8th July 2013 (see Appendix 9.2), which acted as the trial's sponsor. The sponsor funded the Principal Investigator's (Dr Helen Chitty's) salary but no other funding was required. The trial was registered on the ISRCTN trial registry and given a registration number of ISRCTN04448562. The name given to the trial was The VoluVent Trial.

3.3 Regulatory monitoring

The South Tees Hospitals NHS Foundation Trust sponsored the trial. The Research and Development (R+D) department undertook two annual monitoring visits during the trial period. The conduct of the trial and its procedures, such as documentation, training, consent and data collection, were reviewed. Any recommendations made by the R+D department were undertaken. Favourable reports were given by the R+D department on both occasions. An interim report was also submitted to the North-East York Ethics Committee in 2014.

The trial sponsor undertook two monitoring visits on 28th January 2014 and 30th March 2015. The sponsor gave favourable reports with no major concerns raised. Suggestions and requests made by the sponsor were implemented.

3.4 Protocol amendments

Four applications for the following protocol amendments were submitted to the North-East York Ethics Committee and the South Tees Hospitals NHS Foundation Trust Research and Development department during the course of the trial. All applications were written and submitted by the Principal Investigator (Dr. Helen Chitty) and all amendments were given a favourable opinion and approved.

- 23rd July 2013: minor protocol amendment to enable Advanced Neonatal Nurse Practitioners to take consent
- 18th November 2013: substantial protocol amendment to allow the use of deferred consent, recruitment period extended to June 2016.
- 8th September 2014: minor protocol amendment to include the collection of mechanistic ventilator data for the purpose of process evaluation of the trial (see Chapter 5)
- 2nd October 2015: substantial amendment to the Integrated Research Application System (IRAS) form regarding the co-enrolment of infants into other trials. The original IRAS form had been completed correctly but the sponsor requested clarification in the IRAS form that infants enrolled into this trial may subsequently also participate in other studies. This did not require a change to the trial protocol.

3.5 Objectives

The purpose of this single centre RCT was to compare VCV with VG in preterm infants born at less than 34 weeks' gestation with RDS. The aim was to determine whether these infants were ready for extubation faster in the VG group compared to the VCV group.

3.6 Hypothesis

The hypothesis for this trial was that infants in the VG group would be ready for extubation faster than infants in the VCV group. Two previous randomised controlled trials conducted in the same neonatal unit compared VCV with time-cycled pressure limited (TCPL) ventilation in preterm infants with RDS (Sinha et al., 1997; Singh et al., 2006). Those trials used objective 'success' criteria defined *a priori* to standardise the primary outcome. Those criteria represented the level of ventilatory support at which most infants are ready for extubation. In this study, objective 'success' criteria were also defined *a priori* to represent readiness for extubation. Based on those previous data, the research team hypothesised that the use of VG would lead to a 33% reduction in the time taken to reach the 'success' criteria from 23 hours to 15 hours when compared with VCV.

3.7 Primary outcome measure

The primary outcome measure for this study was the duration of time of mechanical ventilation via an endotracheal tube (measured in hours) from study entry until the predetermined 'success' criteria were reached. The 'success' criteria consisted of

- a mean airway pressure of <8 cmH₂O and a fractional inspired oxygen concentration (FiO₂) ≤ 0.35 maintained for six consecutive hours

followed by

- successful completion of a spontaneous breathing test (SBT).

If there was a planned or unplanned extubation prior to reaching the 'success' criteria, after which the infant did not require reintubation for 24 hours, this was

also classed as 'success' and results were analysed on an intention-to-treat basis.

The first two 'success' criteria (mean airway pressure and FiO_2) were chosen because they reflect clinical and physiological parameters at which extubation would be considered as part of standard practice in the study unit. The SBT was used to assess the infants' spontaneous respiratory drive. These objective criteria were used to standardise the primary outcome measure across both arms of the trial. When compared with other measures of minute ventilation in a study of 50 preterm infants, the SBT had a higher sensitivity (97%) and specificity (73%) (Kamlin et al., 2006). Similar tests have been reported and used in previously published studies (Wilson et al., 1998; Gillespie et al., 2003; Gupta et al., 2009).

Data from any infants who died or were transferred to another hospital before reaching the 'success' criteria were censored. This was planned *a priori* and is detailed in the statistical analysis plan (SAP) (see Appendix 9.3)

3.7.1 Measuring the primary outcome

When prospective consent was used, study entry was defined as

- the time of admission (as documented in the medical record) for infants who were intubated before admission to the unit and subsequently randomised to VCV after consent was obtained,
- the time of randomisation (as documented in the medical record) for infants intubated before admission and subsequently randomised to VG after consent was obtained,
- the time of randomisation (as documented in the medical record) for infants intubated after admission to the unit.

When deferred consent was used, study entry was defined as

- the time of admission (as documented in the medical record) for infants intubated before admission and randomised on admission to the unit,
- the time of surfactant administration (as documented on the prescription chart in the medical record) for infants intubated and randomised after admission to the unit.

The time at which all 'success' criteria were reached was the time documented at the end of the successful SBT. Documentation of physiological parameters and timings during this test were done using a specifically designed worksheet demonstrated in Appendix 9.4.

3.8 Secondary outcome measures

The secondary outcome measures chosen were those that reflected short- and medium-term morbidities prior to discharge from hospital in preterm infants who receive mechanical ventilation.

3.8.1 Respiratory outcome measures

- Total duration (in hours) of mechanical ventilation via an ETT until first extubation.
- Requirement for reintubation within 72 hours of extubation (in accordance with the trial protocol).
- Total duration (in hours) of mechanical ventilation via an ETT until successful extubation.
- Pulmonary air leak while receiving mechanical ventilation (including pneumothorax, pneumomediastinum, pneumopericardium, pneumatocele, and pulmonary interstitial emphysema) as reported on a chest x-ray by a Consultant Neonatologist or Paediatric Radiologist.
- Number of episodes of hypocarbia during mechanical ventilation (defined as carbon dioxide tension of less than 4.0 kPa) requiring adjustment of ventilation.
- Total duration (in hours) of non-invasive artificial respiratory support including nasal CPAP, bi-level nasal CPAP and HHFNC.
- Number of infants requiring rescue treatment with high frequency oscillatory ventilation (as decided by a Consultant Neonatologist in accordance with the trial protocol).
- Need for continuous or intermittent supplemental oxygen at a postmenstrual age of 28 days and at 36 weeks' corrected gestational age.

- Bronchopulmonary dysplasia (BPD) requiring home oxygen therapy or continuation of any form of respiratory support at home.

3.8.2 Mortality

- Death before discharge from hospital.

3.8.3 Neurological outcomes

- Severe intraventricular haemorrhage (grades 3 or 4 according to the Papile classification and reported using cranial ultrasonography by a Paediatric Radiologist or Specialist Paediatric Radiographers).
- Periventricular leukomalacia (reported using cranial ultrasonography by a Paediatric Radiologist or Specialist Paediatric Radiographers).

3.8.4 Other outcomes related to prematurity

- Retinopathy of prematurity requiring laser treatment (as diagnosed by a Paediatric Ophthalmologist).
- Patent ductus arteriosus (diagnosed on echocardiogram) requiring medical or surgical treatment (as decided by a Consultant Neonatologist).
- Necrotising enterocolitis (Bell stage 2 or greater).
- Intestinal perforation not due to necrotising enterocolitis.
- Number of confirmed episodes of infection (positive cultures from blood and cerebrospinal fluid at a time when the infant showed clinical signs of infection).

3.9 Serious adverse events

The expected serious adverse events (SAEs) that could be reasonably expected to occur in infants in this trial included:

- death,
- BPD (defined as requirement for supplemental oxygen or positive pressure respiratory support at 36 weeks' corrected gestational age),
- requirement for re-intubation,

- pulmonary air leak during mechanical ventilation, including pneumothorax, pneumomediastinum, pneumopericardium, pneumatocele, pulmonary interstitial emphysema (as reported by a Consultant Neonatologist or Paediatric Radiologist),
- hypocarbia ($pCO_2 < 4.0$),
- pulmonary haemorrhage (as diagnosed by a Consultant Neonatologist)
- necrotising enterocolitis (any stage and diagnosed by a Consultant Neonatologist using clinical and radiological parameters and/or tissue histology),
- intestinal perforation (diagnosed using clinical and radiological parameters and confirmed during surgery),
- intracranial haemorrhage or focal white matter damage (diagnosed using cranial ultrasonography by a Paediatric Radiologist or Specialist Paediatric Radiographer),
- persistent patent ductus arteriosus (diagnosed using echocardiography and requiring either medical or surgical treatment)
- retinopathy of prematurity (any stage and diagnosed by a Paediatric Ophthalmologist)

These SAEs did not require immediate reporting but were recorded prospectively in the medical records and managed by the treating clinician in accordance with standard unit practice. Expected SAEs were recorded on case report forms.

3.10 Trial site

This was a single centre study based at the neonatal unit at The James Cook University Hospital, Middlesbrough, UK. This is a level three neonatal unit that cares for infants of any gestation requiring intensive, high dependency or low dependency care. It does not provide surgical or cardiothoracic services. Infants requiring those services are transferred to other regional surgical centres. In the period during which the trial took place, the unit contained ten intensive care/high dependency cots and 12 special care cots. There were approximately 4,300 infants delivered in the hospital each year during that time period and

approximately 500 admissions per year to the neonatal unit. Infants in other hospitals who require intensive care that could not be provided in their local unit were transferred to the trial site by the regional neonatal transport teams.

For this trial, infants born at The James Cook University Hospital who were admitted to the neonatal unit were referred to as *inborn infants*. Infants who were transferred from other hospitals to The James Cook University Hospital neonatal unit were referred to as *outborn infants*.

3.11 Inclusion criteria

All infants admitted to the trial site were screened for eligibility. Infants were enrolled into this trial if they fulfilled the criteria below:

- born at < 34 weeks' gestation and,
- < 24 hours old at the time of initial intubation and,
- required intubation and mechanical ventilation for RDS and,
- deferred written informed consent was obtained from parents within 36 hours of intubation (after randomisation).

The diagnosis of RDS was based on a combination of clinical signs (respiratory distress or apnoea), radiographic features (reticulogranular appearance with air bronchograms and diminished lung volume), and biochemical evidence of respiratory failure (respiratory acidosis on blood gas analysis).

3.12 Exclusion criteria

Infants were ineligible for inclusion in the trial if they fulfilled any of the criteria below:

- required mechanical ventilation for reasons other than RDS or,
- had a known congenital anomaly likely to adversely affect the respiratory system or life expectancy or,
- written informed deferred consent was not obtained within 36 hours of intubation.

3.13 Consent

Infants were enrolled into the trial only if written informed consent was obtained from the parents after birth. Consent was not sought before birth. Written and

verbal information was offered to parents before birth if they presented to the hospital several hours before delivery but only if it was appropriate to do so. Otherwise it was offered to parents as soon as was appropriate after the delivery.

3.13.1 The initial procedure for obtaining informed consent

Initially eligible infants were enrolled into the trial only if parents had given prospective written informed consent after birth and within 12 hours of their infant's intubation. Before consent was obtained eligible infants were ventilated using VCV as this was the standard ventilatory mode for preterm infants with RDS in the neonatal unit at that time.

However, during the first three months of the trial it became apparent that prospective consent did not allow sufficient time for most parents to make an informed decision about participation. Some parents reported that they needed more than 12 hours to consider the information. Many also stated that they did not want to participate because the possibility of randomisation to VG would lead to a change to their infant's mode of ventilation solely for the purpose of the trial. In the cases of outborn infants, most parents had not arrived at the hospital within 12 hours of initial intubation meaning that they could not be given the opportunity to consider participation in the trial.

Therefore, in order to ensure that the consent process was more appropriate for parents to better enable them to make an informed decision, a protocol amendment was made to enable the use of deferred consent.

3.13.2 A protocol modification to enable the use of deferred consent

In November 2013, the protocol was amended so that deferred consent could be used. This meant that infants born at <34 weeks' gestation and intubated within 24 hours of birth for RDS can now be randomised at the time of admission or at the time of intubation if they have been managed on CPAP initially. Parental consent was then sought after randomisation. The deadline for obtaining written parental consent was 36 hours from the time of intubation. This amendment was implemented after receiving a favourable opinion from the North East-York Ethics Committee and approval from the trial's sponsor, South Tees Hospitals NHS Foundation Trust.

Infants for whom consent was obtained were managed according to the trial protocol. Infants for whom consent was not obtained remained on the mode of ventilation to which they were randomised. Subsequent management depended on the decision of the treating clinicians.

The use of deferred consent in the context of emergency care, both in this trial and in other settings, is discussed further in Chapter 6 Consent. The rationale for the protocol amendment request was that this trial involved the comparison of two types of emergency intervention, both of which were already widely used and considered to be safe, standard treatments. The requirement for timely randomisation of infants was due to the emergency nature of the interventions. In accordance with current legislation (The Medicines for Human Use (Clinical Trials) and Blood Safety and Quality (Amendment) Regulations', 2008) deferred consent was applicable for use in this trial because

- the trial population required urgent treatment with the interventions,
- for the purpose of the trial the interventions were required urgently,
- meeting the requirements for prospective informed consent was not practicable at the time that the infants required the trial interventions,
- an ethics committee had given its approval for the use of deferred consent.

3.14 Management of infants before stratification

Infants admitted to the unit who initially required NIV but not mechanical ventilation all received CPAP support and were treated in accordance with standard unit practice. To minimise bias in the management of these infants who may have subsequently become eligible for the trial, use of HHFNC was not allowed. This was in accordance with standard practice in the unit at the time.

3.15 Stratification

Infants born at <34 weeks' gestation who had been intubated for RDS within the first 24 hours of life were stratified *a priori* into two groups according to their gestational age at birth. One group consisted of infants born at <28 completed weeks of gestation and the other consisted of infants born between 28 and

33+6 weeks' gestation. Infants were randomised separately according to these two stratified groups.

This stratification was chosen because infants born at <28 weeks' gestation are likely to require longer periods of ventilation than those born at 28-33+6 weeks' gestation. Extremely preterm infants (those born at <28 weeks' gestation) have respiratory systems that are usually structurally and functionally more immature than infants born at ≥28 weeks' gestation (Joza et al., 2015). They are also more likely to have a greater degree of surfactant deficiency than more mature preterm infants (Donn et al., 2017b). Their musculoskeletal and neurological systems are more immature, meaning that they are more likely to require mechanical ventilation and are more likely to require it for longer periods of time.

Therefore gestational age was identified as a factor likely to have a large effect on the primary outcome. This stratification was chosen to ensure that randomisation was balanced for this prognostic factor (Lamb et al., 2015).

3.16 Randomisation

In accordance with standards for good conduct in trial design randomisation was achieved using computer generated block randomisation (with fixed block sizes of four) and serially numbered sealed opaque envelopes (Medicines and Healthcare Products Regulatory Agency, 2012; Lamb et al., 2015). Both stratification groups had separate block randomisation sequences. All procedures, including preparation of the envelopes containing the allocated modes of ventilation, were performed by the Deputy Director of the Clinical Effectiveness Unit at South Tees Hospitals NHS Foundation Trust (Medicines and Healthcare Products Regulatory Agency, 2012). He remained independent of the trial throughout.

Some infants did not have radiographic or biochemical evidence of RDS prior to randomisation. These infants included those who had been intubated in the delivery suite and those intubated very shortly after admission to the neonatal unit. If the treating clinician had made the decision to intubate these infants on the basis of clinical signs of RDS, or because extreme prematurity made

surfactant deficiency highly likely, those infants were stratified and randomised to either VG or VCV. If subsequent clinical, radiographic and biochemical analyses were consistent with surfactant deficiency and RDS, those infants remain eligible for inclusion in the trial.

3.17 Devices used

Both VG and VCV were delivered using AVEA[®] ventilators (Carefusion, Yorba Linda, CA). They were used in accordance with the manufacturer's recommendations (Carefusion AVEA[®] ventilator systems operator's manual, L2786, revision M, 2011). Ventilator maintenance was performed by Carefusion engineers. The pneumotachographs used were hot wire anemometers (flow sensors). Variable orifice flow sensors could be used if hot wire anemometers were not available (Avea Crit Care manual). All other devices and equipment used for infants in the trial were the same as those used in clinical practice in the unit. HFOV was delivered using the SensorMedics 3100A (Carefusion, Yorba Linda, CA) device.

3.18 Management of enrolled infants whilst ventilated

Infants were managed according to a protocol that was as rigorous as possible whilst still being pragmatic enough to be feasibly implemented in an intensive care unit. The protocol mandated strict criteria regarding readiness for extubation (the 'success' criteria). It contained detailed guidance on the use of the trial modes of ventilation. Summaries of this guidance were included in the protocol appendices and in each infant's trial pack. These summaries can be found in Appendices 9.5 and 9.6 of this thesis. The protocol also contained details of the standard care of infants and the standard operating procedures to which the trial was subject.

Figure 3-1 and Figure 3-2 show the flow charts used at the cotside for the management of infants on VG and VCV. The relevant version according to the allocated mode at randomisation was included in each infant's trial pack. The clinical teams could therefore refer to them at the cotside.

The use of 'rescue' HFOV was permitted if an infant was deteriorating on the allocated trial mode of ventilation. The recommended criteria for the use of

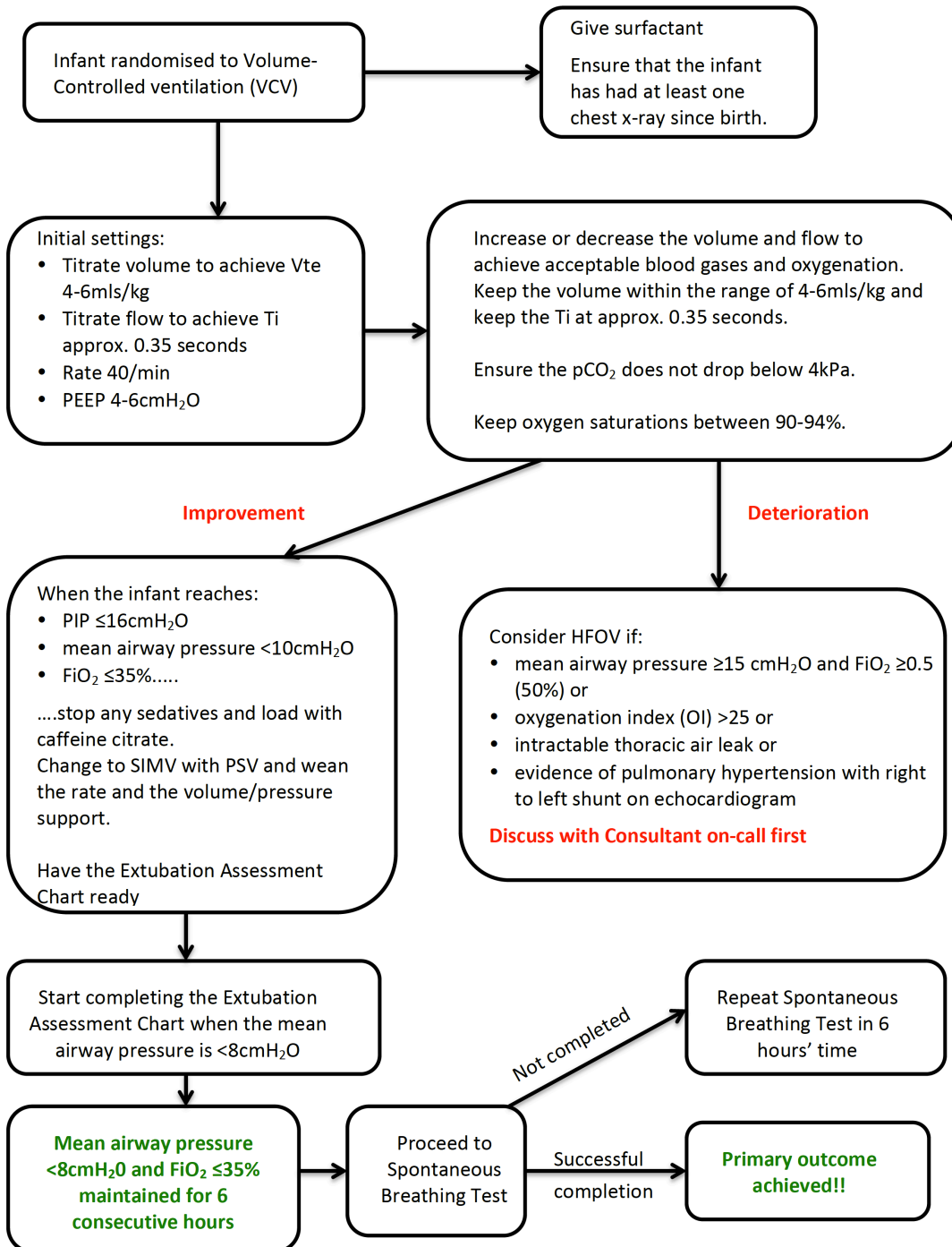
HFOV were included in the protocol and the summaries and flow charts. These criteria, in the context of severe respiratory failure, included:

- mean airway pressure ≥ 15 cmH₂O and FiO₂ ≥ 0.5 (50%) **or**
- oxygenation index (OI) > 25 **or**
- intractable thoracic air leak **or**
- evidence of pulmonary hypertension with right to left shunt on echocardiogram

However, HFOV could also be used without meeting these criteria at the discretion of the treating Consultant Neonatologist depending on the clinical circumstances of each infant.

The VoluVent Trial

Volume-Controlled (volume A/C) ventilation flow chart



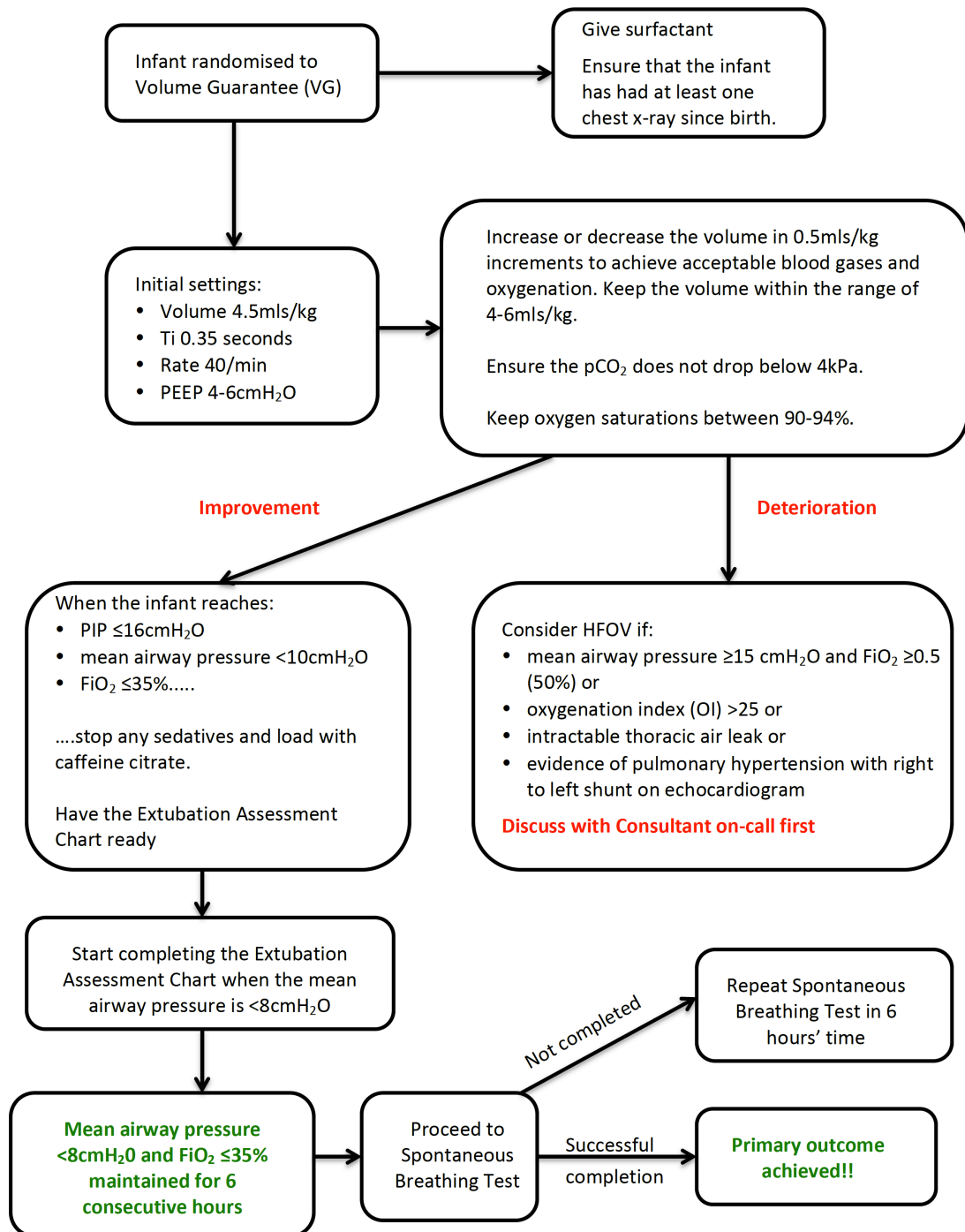
Volume Guarantee or Volume-Controlled ventilation, VG flow chart, version 1, 15th July 2013

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Figure 3-1 Cotside flow chart for management of infants randomised to VCV

The VoluVent Trial

Volume Guarantee flow chart



Volume Guarantee or Volume-Controlled ventilation, VG flow chart, version 1, 15th July 2013

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Figure 3-2 Cotside flow chart for management of infants randomised to VG

3.19 Adjunctive therapies

Two adjunctive therapies were specified in the trial protocol. Others were not specified in the trial protocol and were used when the treating Consultant Neonatologist deemed them to be necessary. The decision to institute these therapies was often made as a joint decision between two or more of the unit's Consultants Neonatologists.

3.19.1 Adjunctive therapies specified in the protocol

- All infants enrolled into the study received at least one dose of exogenous surfactant via the endotracheal tube after intubation. Further doses of surfactant were given if deemed necessary by the treating clinicians. The surfactant used was CUROSURF® (poractant alfa, Chiesi Farmaceutici SpA).
- All infants enrolled into the study received a loading dose of caffeine citrate (20mg/kg) prior to extubation. This was usually given early in the infant's course in accordance with unit practice (Davis et al., 2010). It was given before the mean airway pressure fell below 8cmH₂O whenever possible. The infants then received daily doses of maintenance caffeine citrate (5-10mg/kg). This was given either enterally via a nasogastric tube or intravenously. Maintenance caffeine citrate was continued until at least 34 weeks' corrected gestational age.

3.19.2 Adjunctive therapies given according to standard unit practice

These therapies can affect an infant's respiratory course but, due to the pragmatic nature of the trial, were not mandated in the trial protocol. The reasons for this are discussed further in Chapter 7.

- Infants with patent ductus arterioses that required medical treatment were treated with three to five doses of intravenous ibuprofen. Those that required surgical ligation were transferred to the regional cardiothoracic centre for surgery as a day case and were transferred back to the unit the same day. During transfer and during surgery they received modes of ventilation that were outwith the trial protocol. These include asynchronous PLV from the transport cot ventilator during transfer and pressure-controlled ventilation using a Daegar Primus® ventilator during the operation. The duration of

time during which they received other modes of ventilation was included in time-to-event analyses for primary and secondary outcomes.

- Dexamethasone was used to facilitate weaning of ventilation for infants who became ventilator-dependent and for whom weaning proved difficult. These infants received dexamethasone according to the trial protocol used by the investigators of the 'Dexamethasone: A Randomised Trial' (DART) study (Doyle et al., 2006). They received more than one course, or prolonged courses, if these were felt to be necessary by the treating Consultant Neonatologist. The use of dexamethasone had potential to affect the primary outcome in the few infants who received it. Therefore it was prospectively defined as a covariate and was analysed using multivariable analysis and a Cox proportional hazards model.
- Ventilated infants did not routinely receive sedation or muscle relaxant medication at the trial site. As this protocol was a pragmatic one the use of sedation or muscle relaxants were not specifically mandated. Infants who received sedation during the first period of ventilation (prior to reaching the 'success' criteria) received intravenous morphine sulphate either as a bolus or as an infusion. The 'success' criteria included the use of a SBT. This was only performed if an infant had not received any sedation for at least six hours. If sedation had been administered during that time, the SBT was deferred until six hours after the sedation had been administered.
- Diuretics were not used routinely in the unit for infants requiring prolonged respiratory support. Therefore their use was not specified in the trial protocol

3.20 Contamination

No crossover between trial modes was allowed. Infants enrolled into the trial could receive only the mode of ventilation to which they were randomised (either VG or VCV) or 'rescue' HFOV. Other modes of ventilation were not permitted.

3.21 Minimisation of bias

The interventions in this trial were not masked as it was not considered practical or safe to blind the researchers or clinicians to the modes of ventilation being investigated. Therefore researchers and clinicians were all aware of the modes to which each infant had been randomised. This had the potential to introduce

performance bias. Therefore, other measures were put in place to aim to minimise bias. These included:

- the design of a prospective RCT with a standardised comparison group (VCV) to measure the efficacy of the intervention in the intervention group (VG),
- the use of ongoing training for all clinical team members to minimise performance bias,
- the use of standardised cotside trial packs for each infant containing information on management of each infant according to the allocated mode of ventilation,
- the use of block randomisation to minimise selection bias and aim for a balance of prognostic factors,
- the aim of the clinical and research teams to approach all parents wherever possible to minimise selection bias,
- the design of a detailed trial protocol to minimise performance bias,
- the use of an objective primary outcome measure to minimise detection bias,
- the use of a pre-defined SAP to minimise detection and reporting bias,
- the use of standardised follow up and the aim to achieve complete follow up and data collection in order to minimise attrition bias. The primary outcome was designed such that complete data collection for that outcome could be achieved.

3.22 Management of infants after extubation

Almost all infants received CPAP for non-invasive respiratory support after extubation. This was administered using the Infant Flow Driver device (Infant Flow® LP nCPAP system, Carefusion, Yorba Linda, CA). The starting pressure was set at 6 cmH₂O after extubation. Infants for whom CPAP was considered inappropriate (for example, infants who had had a pneumothorax) could receive HHFNC. Non-invasive respiratory support was administered at the treating clinicians' discretion.

3.23 Data collection

All infants were screened for eligibility on admission. A baseline assessment of eligibility form was completed for all infants born at <34 weeks' gestation and admitted to the neonatal unit in order to determine the number of infants who were eligible but not enrolled as well as the number of infants of the same gestational age who were ineligible. The reasons for non-enrolment were recorded anonymously and included in documentation, presentation and publication of results in keeping with the CONSORT 2010 Statement on transparent and complete reporting of randomised trials (Schulze et al., 2010).

All data were collected prospectively on trial-specific data collection forms. An example of a data collection form is shown in Appendix 9.7.

3.24 Statistical considerations

3.24.1 Trial oversight review

As this was a pilot trial the sponsor (South Tees Hospitals NHS Foundation Trust) confirmed that a formal interim analysis by a Data Safety and Monitoring Committee was not required. However, an external trial oversight review was undertaken by an independent statistician and an independent clinical reviewer. The independent statistician was from the Institute for Health and Society's Biostatistics Research Group at Newcastle University. The clinical reviewer was a Consultant Neonatologist from Birmingham Heartlands Hospital.

The statistician undertook interim analyses of data from the first 50 enrolled infants. The statistician received coded data on:

- maternal and neonatal characteristics,
- delivery details,
- respiratory and ventilation parameters at trial entry,
- primary outcome data.

These data were coded so that the statistician was blinded to the allocated modes of ventilation. Version 6 of the SAP, dated 17th July 2015, was used to undertake the independent interim analyses which were reported on 21st September 2015. The report of these analyses was then sent to the clinical reviewer who reviewed the data. The reviewer produced a favourable report,

dated 15th January 2016, It contained recommendations regarding the sample size calculation. This report is included in Appendix 9.8.

The trial oversight report was reviewed by the Principal Investigator and supervisors. At this stage it remained coded so that the research team were blinded to treatment allocation in the interim analyses. On the basis of the report, the SAP was amended and updated. A final version was finalised on 8th July 2016 and is included in Appendix 9.3 of this thesis. Final analyses of trial data from all infants were only undertaken once all infants had completed the trial and data collection was complete.

3.24.2 Sample size calculation

This section describes how the sample size was determined when the trial was originally designed. In summary, the sample size was originally based on data reported in a study by Singh et al. (Singh et al., 2006). In that paper the primary outcome data were reported as mean values. Therefore, when The VoluVent Trial was designed in 2013, parametric tests were used to calculate the sample size (see Section 3.24.3).

However, the trial oversight reviewer identified that the primary outcome data were likely to be non-normally distributed. Therefore, a statistical approach based on Jung's methodology (Jung, 2008) for randomised phase II trials with a prospective control arm was used. This is discussed in further detail in Section 3.24.4.

3.24.3 Original sample size calculation

Data from two previous studies undertaken at the trial site (Sinha et al., 1997; Singh et al., 2006) were used as references with which to determine the original sample size.

In the first of the two previous studies, VCV was compared with PLV in preterm infants with RDS (Sinha et al., 1997). Fifty infants (25 in each arm) weighing $\geq 1200\text{g}$ were randomised to either VCV or PLV. Predetermined 'success' criteria were used as primary outcome measures (time to achieve an alveolar-arterial oxygen gradient of $<13\text{ kPa}$ or mean airway pressure of $<8\text{ cmH}_2\text{O}$, maintained for $>12\text{ hours}$). In the VCV group, the mean (SD) time taken to

reach the 'success' criteria was 65.5 (55.7) hours. For infants in the PLV group the mean (SD) time was 125.8 (131.8) hours, $p < 0.001$).

In the second trial, Singh *et al.* (Singh *et al.*, 2006) compared VCV and PLV in smaller and more premature infants using the same 'success' criteria. One hundred and nine infants (57 in one arm and 52 in the other arm) born between 24 and 31 completed weeks' gestation and weighing between 600 and 1500g were recruited. Although there was no significant difference between the two groups in the time taken to meet the 'success' criteria, infants assigned to VCV achieved the criteria faster than infants in the PLV group (mean time of 23 hours versus 33 hours respectively, $p = 0.15$). A sub-group analysis showed that in infants weighing $< 1000\text{g}$, VCV significantly reduced the time taken to achieve the 'success' criteria compared with PLV (mean time of 21 hours and 58 hours respectively, $p = 0.03$).

Using known values from those two published trials, a one sample Student's *t*-test was used to calculate the sample size for The VoluVent Trial. This is demonstrated in Table 3-1.

	Sinha <i>et al</i> (1997)	Singh <i>et al</i> (2006)
Known mean value of time to reach 'success' criteria in VCV group	65.6 hours	23 hours
Standard deviation of the known value	55.7	19.26
Reduction in time to reach 'success' criteria (effect size)	33%	33%
Mean value if a 33% reduction in time to 'success' criteria occurred in VG group	43.952 hours	15.41 hours
2-sided alpha	0.05	0.05
Power	0.8	0.8
Sample size	52 in each arm	51 in each arm

Table 3-1 Determination of the sample size using data from previous studies

A decision was made to use the data from Singh *et al*'s study (Singh *et al.*, 2006) on which to base the sample size calculation for The VoluVent Trial. The rationale for this was that the trial population and the clinical practices (including

use of maternal antenatal steroids and postnatal surfactant) reported in the trial by Singh et al. (Singh et al., 2006) more closely reflect current practice than those of Sinha et al. (Sinha et al., 1997).

The hypothesis for The VoluVent Trial was that, because VG aims to target tidal volumes on a breath-by-breath basis, the time taken to reach the 'success' criteria would be shorter in the VG group. Therefore, a sample size of 102 infants (51 in each arm) was needed to show a 33% reduction in the time taken to reach the 'success' criteria from 23 hours in the VCV group to 15 hours in the VG group with a 2-sided alpha of 0.05 and a power of 80%. To account for a 10% withdrawal rate, the overall recruitment target was a sample size of 112 infants.

3.24.4 Retrospective sample size calculation using non-parametric tests

As explained above the primary outcome data reported by Singh et al. (Singh et al., 2006) were reported as mean values. Therefore, a parametric test was used for the original sample size calculation for this trial. However, the trial oversight review identified that the data from The VoluVent Trial was likely to be non-normally distributed. The independent reviewer recommended a retrospective calculation using a log-rank analysis of the data by Singh et al. (Singh et al., 2006) to determine how to present the final analysis of data.

Therefore a retrospective sample size calculation with a log-rank test was performed using the data reported by Singh et al. (Singh et al., 2006). The software used was Sample Size Tables for Clinical Studies Software Program, version 1.0, July 2008. The proportions were based on taking an end point of 48 hours on the Kaplan-Meier curve from the paper by Singh et al. (Singh et al., 2006) and comparing the associated cumulative survival points. At 48 hours, the cumulative survival in the VCV arm was approximately 0.05 and in the TCPL arm it was 0.15. If the expected number of events (number of infants reaching 'success' criteria) in each arm was 52 (based on the original sample size calculation for The VoluVent Trial), based on a power of 80%, an allocation ratio of 1:1, a first proportion of 0.05, a second proportion of 0.15 and significance level 0.05, the sample size would need to be 178.

Therefore the planned sample size of 112 infants for The VoluVent Trial was not large enough to have sufficient power to demonstrate statistical significance. A different approach was then considered.

3.24.5 Analysis of results using differences in response rates.

A different approach to statistical analysis of data from this trial is that described by Jung (Jung, 2008) for design of randomised phase II trials with a prospective control arm. This involves an initial stage of research that Jung refers to as the “single-stage” element. This equates to a pilot trial in which response rates to an intervention in the control arm and in the comparison arm are compared. If the difference between the response rates is sufficiently large that it reaches a pre-determined level at the end of that initial stage, the trial team then proceeds to a larger trial to aim for a definitive result. If the difference between the two arms is not sufficiently large and does not reach the pre-determined level it is unlikely that there is a difference between the two arms and further research is not undertaken.

Using this approach to interpret the data by Singh et al. (Singh et al., 2006), the response rates can be defined as the proportion of infants who had reached the ‘success’ criteria at a particular time point. According to the Kaplan-Meier curve reported by Singh et al. (Singh et al., 2006), the cumulative survival (the proportion of infants that had *not* reached the ‘success’ criteria) at 48 hours was approximately 0.05 in the VCV arm and 0.15 in the TCPL arm. This also meant that the proportion reaching the ‘success’ criteria by 48 hours was 0.95 in the VCV group and 0.85 in the TCPL group. The sample size for that trial was 109, meaning that the response rate was approximately 85% of infants in the TCPL group and approximately 95% of infants in the VCV group at 48 hours. In terms of clinical relevance this meant that approximately 10 more infants had met the ‘success’ criteria by 48 hours in the VCV group compared to the TCPL group. This is an important clinical difference between the two groups.

The methodology described by Jung (Jung, 2008) was considered appropriate for The VoluVent Trial because, as a pilot trial, its aim was to inform the direction of a larger trial or body of research rather than provide a definitive result.

3.25 Descriptive analyses of the primary outcome measure

The detailed SAP is included in Appendix 9.3. This was written and in place prior to analysis of any data. In summary, initial planned analyses of the primary outcome measure included summary statistics including:

- the display of Kaplan-Meier time-to-event curves,
- the presentation of median time-to-event values with interquartile ranges,
- the use of Cox proportional hazards models to calculate hazards ratios and 95% CIs,
- response rates (numbers of infants reaching the 'success' criteria) by 48 hours.

3.26 Analysis of covariates

A Cox proportional hazards model was used to investigate the effects of covariates on the primary outcome. Univariable and multivariable analyses were undertaken. The results were presented as hazards ratios with CIs. The covariates likely to affect the primary outcome were specified *a priori* in the SAP and included:

- the administration of maternal antenatal steroids prior to delivery,
- the administration of postnatal steroids to facilitate extubation,
- surgical management of a patent ductus arteriosus.

3.27 Subgroup analyses

Data from all infants in the trial were analysed and presented. Subgroup analyses were also undertaken as planned *a priori* in the SAP. Infants were stratified into two groups according to gestational age at birth; those born at <28 weeks of gestation and those born between 28 – 33+6 weeks of gestation. Data from both stratified groups were presented and described separately but were not tested for significance. Descriptive analysis of primary outcome data on inborn infants was also planned. This was undertaken because inborn infants were managed according to the trial protocol throughout, whereas outborn infants were likely to receive other modes of ventilation before admission to the trial site.

3.28 Descriptive analyses of the secondary outcome measures

Analyses of secondary outcome data were planned as descriptive analyses. The trial was not powered to detect significant differences in these outcomes measures. Normally distributed data were analysed using an unpaired t-test. Non-parametric tests (such as Mann Whitney U test or Wilcoxon rank-sum test) were used if data were not normally distributed. Presentation of continuous data was planned as mean values with standard deviations. For non-normally distributed data, presentation of data as median values with inter-quartile ranges was planned. Categorical data were compared using chi-squared contingency table tests or a Fisher exact test. Dichotomous outcomes were presented as odds ratios with CIs.

3.29 Intention-to-treat definition

Analyses were planned on an intention-to-treat basis. Initially, when prospective consent was planned, the intention-to-treat definition included comparing outcomes for all infants regardless of whether they received the allocated treatment mode. However, after the introduction of deferred consent, a strict intention-to-treat definition could no longer be applied as data from some randomised infants could not be analysed as consent was not obtained. Therefore, the intention-to-treat definition had to be modified to include only infants who were eligible, had been randomised, and for whom consent had been obtained.

3.30 Statistical software

All statistical analyses were carried out using an SPSS statistical software package (IBM SPSS Statistics for Macintosh, version 20.0.0, 2011. Armonk, NY: IBM Corp).

3.31 Duration of the trial

Infants remained in the trial until discharge from hospital, or until death if they died before discharge. Secondary outcome data were collected until either death or discharge from hospital. The active phase of the trial was planned to end when the last remaining infant had died or been discharged from hospital. Data collection and analysis, compilation of reports, presentation and

publication in peer-reviewed journals were planned to continue after the active phase.

The planned recruitment period was based on previous data from the trial site. These are shown in Table 3-2.

Year	Number of infants born at 34 weeks' gestation requiring ventilation at the trial site
January - December 2010	97
January - December 2011	88
January - December 2012	92

Table 3-2 Data on ventilated infants born at <34 weeks' gestation at the trial site from 2010 - 2012

From January 2010 to December 2012 there were 277 infants born at <34 weeks' gestation who required ventilation at the trial site. This produced a mean of 7.7 potentially eligible infants per month. The anticipated recruitment rate was five infants per month into the trial. Recruitment was therefore expected to take 18 - 24 months.

Chapter 4 Results

4.1 Introduction

The results of The VoluVent Trial are discussed in this chapter. The trial's SAP was used as the framework for presentation of the results. In the SAP, some of the template tables indicated that mean values with standard deviations (SD) would be presented. In this chapter, the tables do present normally distributed data as mean values with SDs. However, if the data were not normally distributed, they were presented as median values with interquartile ranges (IQR).

4.2 Recruitment

Recruitment started on 22nd July 2013, and was completed on 6th December 2015. This was longer than the initial expected recruitment period of 18 - 24 months due to the challenges in seeking informed parental consent during the first four months of the trial, and due to an increase in the use of non-invasive ventilation in the trial unit (Garg, 2014). The final patient remaining in the trial was discharged from hospital in April 2016 and data collection was completed shortly after.

During the trial period, 377 infants born at less than 34 weeks of gestation were screened for eligibility. Infants were included in the trial if they met all of the inclusion criteria, including the need for written parental consent.

Therefore, only infants for whom consent was obtained were included in the trial. Figure 4-1 illustrates the reasons for screening and recruitment in accordance with CONSORT guidelines (Schulz et al., 2010).

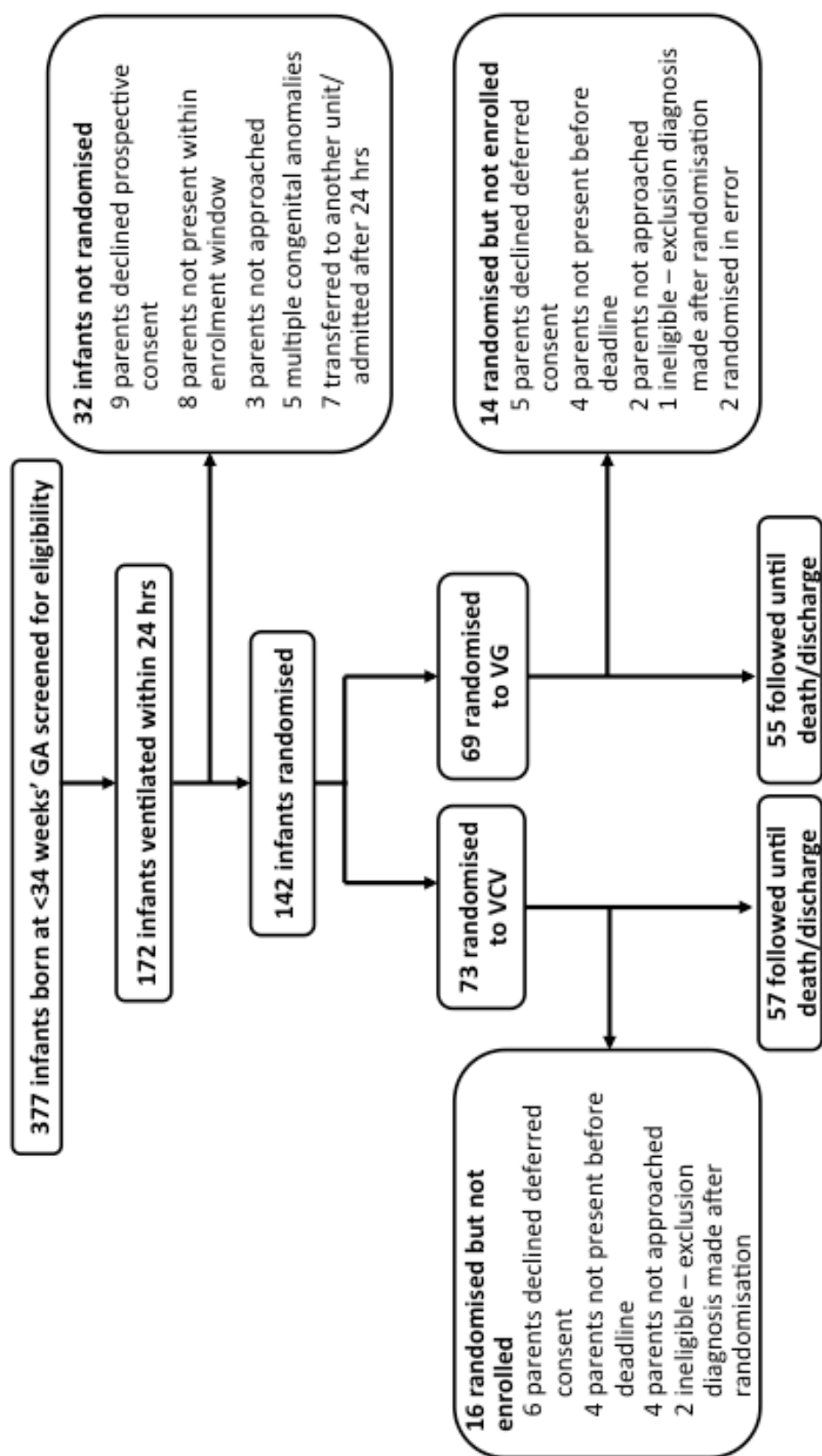


Figure 4-1 CONSORT diagram demonstrating the number of infants screened for eligibility, randomised, and enrolled into The VoluVent Trial.

4.2.1 Recruitment before and after the introduction of deferred consent

4.2.1.1 Before the introduction of deferred consent

Recruitment was expected to take 18 - 24 months. It was anticipated that five infants per month would be recruited. However, as shown in Figure 4-2 the actual number of ventilated infants born at <34 weeks' gestation and admitted to the trial site was lower than expected. Only six out of 24 potentially eligible infants were recruited in four months. This equates to a recruitment rate of 1.5 infants per month. These infants were all inborn infants. Three of these infants were triplets whose parents had received written and verbal information about the trial at an earlier antenatal appointment. Therefore, only four sets of parents gave consent for the trial before the change in the consent method.

4.2.1.2 Reasons for the initially low recruitment rate before the introduction of deferred consent

Between July and November 2013, prospective consent was used. This meant that an infant could only be randomised if parents had given written informed consent within 12 hours of intubation. Prior to consent and randomisation, potentially eligible infants received VCV after birth in accordance with the protocol as this was standard unit practice.

The clinical and research teams aimed to approach as many parents as possible before delivery if appropriate. Despite this the recruitment rate remained lower than expected. This was for three main reasons.

1. The use of non-invasive respiratory support such as CPAP in very preterm infants had become more established as standard practice at the trial site. CPAP was initiated in many infants who showed good respiratory effort shortly after birth, even in those infants born ≥ 27 weeks' gestation. Many of these infants subsequently did not require mechanical ventilation. Of those infants that did require mechanical ventilation, some were intubated after 24 hours of age. As such they were not eligible for the trial.
2. More parents declined prospective consent than expected. Parents were not asked to give their reasons for declining consent. However, many did spontaneously volunteer their reasons. Some did not want their infants to

take part in a research study. However, for many, their reasons for declining were related to the consent process. Some of these reasons are listed here.

- There was not enough time before the consent deadline in which parents could consider the trial information or make a decision.
- Some mothers remained affected by sedative medications received before or at the time of delivery. Therefore they were not able to consider the trial information in order to make an informed decision.
- Parents knew that randomisation may lead to a change in their infant's mode of ventilation. Some parents did not want the ventilator mode to be changed on the basis of their decision to give consent to the trial.
- Some parents of twins or triplets did not want their infants randomised to different modes of ventilation.

3. Eight eligible infants admitted to the trial site during this time were outborn infants whose parents were not present at the trial site within 12 hours of intubation. These eight infants represented 33% of eligible infants admitted to the trial site at that time. Their parents had to travel from the hospital at which their infants were born to the trial site. It could take several hours for parents to travel or be transferred between hospitals. The mothers of these infants were usually still receiving postnatal inpatient care themselves, meaning that they could not be transferred between hospitals quickly. Therefore, one third of the parents of eligible infants could not be approached because they were not present prior to the consent deadline.

It was therefore apparent that prospective consent was not an appropriate method of consent for this type of trial. Parents who may, under different circumstances, be willing to consider their infant's participation in a trial were not able to do so when asked to consider the trial information within a narrow timeframe shortly after the birth of their preterm infant. The consent process was deterring many from being able to make a decision about their infant's participation.

Therefore the research team sought approval for a major amendment to the protocol so that deferred consent could be used. They also sought an extension to the recruitment period of 12 months. This extension was requested to aim to ensure that the trial recruited the planned sample size.

4.2.2 Change to the consent method

On 18th November 2013, the North East-York regional ethics committee granted a favourable opinion for a protocol amendment involving the use of deferred consent. South Tees Hospitals NHS Foundation Trust Research and Development department also approved the amendment and deferred consent was used from that point onwards. A request to extend the recruitment period to June 2016 was also approved.

As illustrated in Figure 4-2, the recruitment rate improved with 107 infants being recruited over the next 25 months. This equates to a recruitment rate of 4.28 infants per month after the introduction of deferred consent.

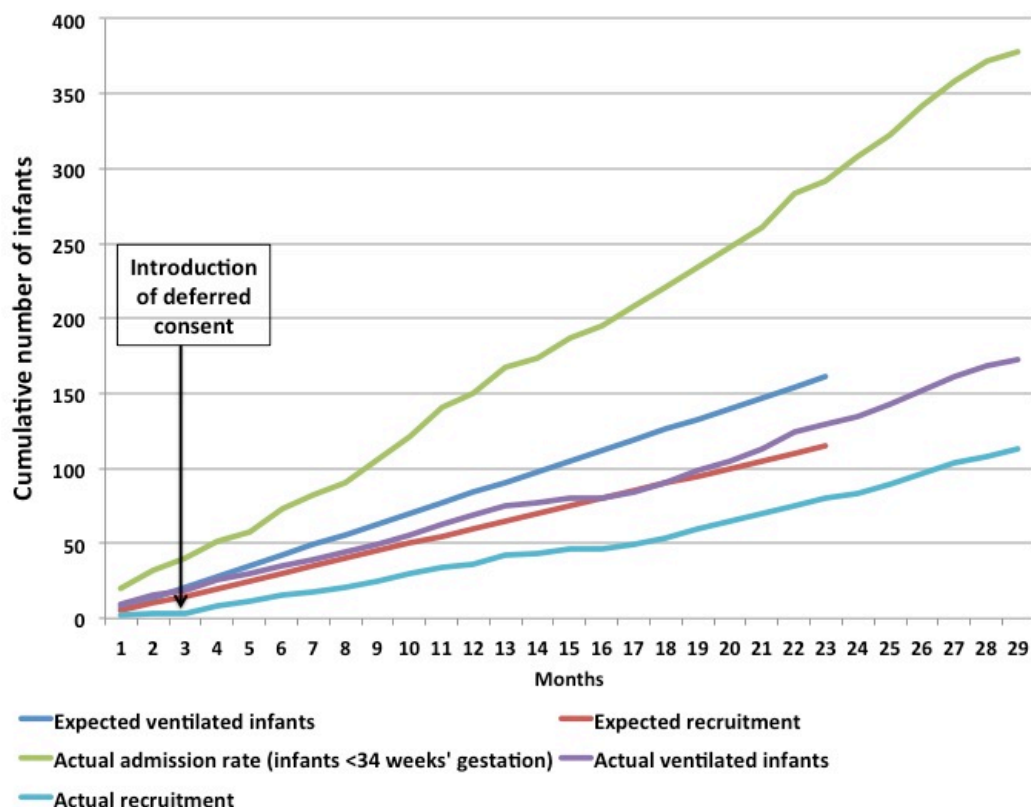


Figure 4-2 Graph demonstrating expected versus actual rates of ventilated infants and of enrolled infants.

4.2.3 Recruitment during the entire recruitment period

Recruitment continued for a total of 29 months and was completed in December 2015 when 113 infants had been enrolled (although one infant had been withdrawn due to ineligibility). During the entire recruitment period, 172 infants

were ventilated, giving an overall mean of 5.9 potentially eligible infants admitted to the trial site per month. A mean of 3.9 infants per month were recruited.

Table 4-1 shows the comparisons of data from the trial's screening log. It shows that the change in the consent method improved the recruitment of eligible infants. There was a marked reduction in the number of parents declining consent, as well as the number of parents who were not present within the consent deadline because their infants were outborn infants.

This table is specifically used to demonstrate the impact of deferred consent on recruitment. Therefore it includes the infant who was enrolled but later withdrawn.

	Before the change in consent process	After the change in consent process	Total recruitment period
Months of recruitment, n	4	25	29
Infants born at <34 weeks' gestation, n	47	330	377
Infants born at <34 weeks' gestation and did <i>not</i> receive ventilation within 24 hours of birth, n	22	172	194
Infants born at <34 weeks' gestation and <i>did</i> receive ventilation within 24 hours of birth, n	24	148	172
Infants randomised, n (%)	6 (25)	136 (92)	142 (82.6)
Infants enrolled, n (%)	6 (25)	107 (78.7)*	113 (65.7)*
Parents declined consent, n (%)	9 (37.5)	11 (7.4)	20 (11.6)
Parents not present at the trial site before the consent deadline because infants were outborn, n (%)	8 (33.3)	8 (5.4)	16 (9.3)
Parents not approached, n (%)	3 (12.5)	6 (4.1)	9 (5.2)

Table 4-1 Comparisons of eligibility screening log data before and after the change in consent method

n, number; %, proportion of the infants who did receive ventilation within 24 hours of birth. To demonstrate the impact of deferred consent on recruitment the numbers of enrolled infants here also include the infant who was enrolled

and later withdrawn from the trial. Therefore these numbers appear different to those in the CONSORT diagram in Figure 4-1.

4.2.4 Other challenges affecting recruitment

Despite the improvement in recruitment rate after the change in the consent method, there were still fewer eligible infants and fewer recruited infants than had been anticipated. The reasons for this are listed here:

- **Infants who did not receive mechanical ventilation within the first 24 hours of life:** Figure 4-1 demonstrates that 205 infants were born at <34 weeks' gestation but did not receive mechanical ventilation within the first 24 hours of life. These infants were therefore not eligible for the trial. They represent 51.4% of all infants born at <34 weeks' gestation and screened for eligibility for the trial. Specific data on further clinical management of these infants were not collected for the purpose of this trial. However, the broad categories regarding the respiratory management included:
 - no respiratory support required at any time,
 - supplemental oxygen only required,
 - non-invasive respiratory support only required.
 - non-invasive respiratory support only required initially but mechanical ventilation was received at some time after 24 hours of age.

As specific data on these infants were not collected for this trial, the proportions of infants managed in each category are not known. However, the use of non-invasive respiratory support in very preterm infants (infants born between 28 and 31+6 weeks' gestation) had become more established as standard practice at the trial site over recent years.

- **Infants of parents who had not yet arrived at the trial site:** 16 infants were not enrolled because their parents were not present in the neonatal unit before the consent deadline. Eight of these infants were admitted before the introduction of deferred consent. At that time, the protocol stated that consent had to be sought within 12 hours of intubation. The other eight infants were admitted to the trial unit after the introduction of deferred consent at which point consent had to be

sought within 36 hours of intubation. All of these 16 infants were outborn infants.

4.2.5 Reasons for randomisation but non-enrolment

Twenty-nine infants were randomised but not enrolled into the trial. For most, this was because deferred parental consent was not sought or obtained. The specific reasons are given below.

- Two infants ventilated after 24 hours of life were randomised in error. As they did not meet the eligibility criteria consent was not sought and they were not enrolled into the trial. Both infants had been randomised to receive VG.
- Two infants were initially randomised appropriately to one of the trial modes of ventilation but were then diagnosed with major congenital anatomical anomalies affecting the respiratory system and potentially affecting life expectancy. As this was one of the exclusion criteria these infants' parents were not approached for consent. One of these infants had been randomised to VG and one had been randomised to VCV.
- Twenty-five infants were randomised appropriately but subsequently deferred consent was not obtained. They did not therefore meet the inclusion criteria and were not enrolled into the trial. Two of these infants died before consent could be sought; one had been randomised to VCV and the other had been randomised to VG. The CONSORT diagram shown in Figure 4-1 demonstrates that the reasons for not obtaining consent were balanced between the two groups.

4.2.6 Infant withdrawn from the study

One infant was randomised on the basis of meeting all the inclusion criteria after birth. This was confirmed prospectively by the clinical team and later by the research team. The infant was enrolled into the trial when deferred consent was obtained. However, several days later, this infant was diagnosed with a condition consistent with one of the exclusion criteria. This congenital condition had not been suspected previously and was one that substantially altered the infant's intrinsic respiratory condition. In addition, over time, management of this infant within the trial protocol contributed to the infant's clinical instability. The

treating clinician and research team agreed that the infant should be withdrawn from the study at that point to prevent further clinical instability. After that point, the infant was no longer managed according to the trial protocol. The infant had not reached the 'success' criteria by this point. The parents were informed of the decision to withdraw the infant from the trial.

After careful consideration the research team decided that data from this infant should be excluded from the analysis. This judgement was made because this infant's condition made him/her inherently different from the rest of the trial population. Inclusion of this infant's data in the analysis would bias the results because the continued need for ventilation was due to the underlying condition and not primarily due to ongoing lung disease associated with prematurity. Therefore previously collected data on this infant were destroyed, no further data were collected and no data from this infant were analysed. The parents were informed of this decision.

The SAP stated that data would be analysed on an intention-to-treat basis for all infants from whom consent was obtained. Therefore this was a protocol deviation (Abraha et al., 2010). However, this was a pilot trial aiming to investigate the effects of VTV on a target population that was representative of preterm infants with RDS. This infant was not representative of the target population and excluding his/her data was acceptable in the context of a pilot trial (Giangregorio et al., 2015). This is discussed further in Section 7.5.5 of Chapter 7 Discussion.

Therefore, the analysis of data from this trial was done on a modified intention-to-treat basis (Abraha et al., 2010) although it shall be referred to as intention-to-treat during this thesis. A discussion of its strengths and limitations is included in Section 7.5.5 of Chapter 7 Discussion.

4.2.7 Delays in randomisation

In two eligible infants, there was a substantial delay in randomisation.

1. In one case, because the unit was busy, the infant was initially started on VCV with a plan to randomise shortly afterwards. Due to an oversight, the clinical team did not realise that randomisation had not occurred. The infant remained on VCV for 13 hours and 55 minutes until randomisation.

The infant's allocated mode of ventilation was VG therefore the mode of ventilation was changed to VG at the time of randomisation. The infant's primary outcome was therefore measured as the duration of time from the point of randomisation until the time at which the 'success criteria' were met.

2. In the second case, the team consisted of new medical personnel who misinterpreted the protocol and thought that only the research team could randomise the infant. The infant was born at night and received VCV for seven hours and 40 minutes until the research team became aware the following morning. The infant was then randomised to the allocated mode of VCV. All other care of the infant prior to randomisation had been in accordance with the protocol. The infant had not yet reached the success criteria. Therefore, for this infant, the primary outcome was measured as the duration of time from starting VCV (not from the time of randomisation) until the time at which the 'success criteria' were reached.

For the first infant, randomisation led to a change in the mode of ventilation and therefore the delay in randomisation substantially affected the measurement of the primary outcome. For the second infant, because randomisation did not lead to a change in the mode of ventilation, the primary outcome was not affected. For both infants, the delays were recorded in the case record forms as protocol deviations.

4.2.8 Co-enrolment

In October 2015, an amendment was made to the IRAS form at the request of the trial's sponsor during a monitoring visit. The IRAS form had originally been completed correctly to state that infants being enrolled were not already enrolled in other studies. However, the sponsor requested clarification in the IRAS form that infants enrolled into this trial may subsequently also participate in other studies. This did not require an amendment to the protocol. Due to the timeframes in which consent had to be sought, consent for this trial was always sought before that of any other.

4.2.9 Practical strategies regarding co-enrolment

Prior to the introduction of any new study within the unit the research team, the Consultant Neonatologists and senior nursing team discussed the potential challenges regarding co-enrolment. Any studies that were deemed to risk introducing bias, safety concerns or protocol contamination to studies already underway were not undertaken at that time.

Six other research studies were undertaken at the trial site during The VoluVent Trial's recruitment period. Not all of these studies took place at the same time and not all infants were enrolled into all studies. These studies are listed below.

1. A multi-centre RCT comparing different thresholds for platelet transfusion in preterm infants (The PLaNeT-2 Trial, ISRCTN registry number 87736839, <https://doi.org/10.1186/ISRCTN87736839>). The primary outcome was the proportion of infants who die or experience a major bleed up to and including day 28 of life.
2. A single centre RCT comparing methods of measuring blood pressure in preterm infants (The NiDOP study, ISRCTN registry number 36164200, <https://doi.org/10.1186/ISRCTN36164200>). The primary outcome was the correlation of blood pressure measurements between three different methods.
3. A multi-centre RCT comparing speeds of increasing enteral feeds in preterm infants (The SiFT Study, ISRCTN registry number 76463425, <https://doi.org/10.1186/ISRCTN76463425>). The primary outcome was survival free from moderate or severe neurodisability at 24 months' corrected gestational age.
4. A multi-centre RCT comparing lactoferrin with a placebo in preterm infants (The ELFIN study, ISRCTN registry number 88261002, <https://doi.org/10.1186/ISRCTN88261002>). The primary outcome was the incidence of late-onset infection prior to discharge from hospital.
5. A multi-centre RCT comparing ibuprofen with a placebo in preterm infants (The Baby-OSCAR Trial, ISRCTN registry number 84264977, <https://doi.org/10.1186/ISRCTN84264977>). The primary outcome was death or BPD at 36 weeks' corrected gestational age.

The above studies were deemed to be compatible with The VoluVent Trial. An independent expert clinical researcher from The University of Melbourne was consulted regarding The Baby-OSCAR Trial. His advice was that recruitment to The Baby-Oscar Trial would not bias the results of The VoluVent Trial, which was already nearing the end of recruitment. Only one infant enrolled into The VoluVent Trial was also co-enrolled into The Baby-OSCAR Trial.

Two RCTs were not undertaken at the trial site as the research team deemed that the protocols were not compatible with that of The VoluVent Trial. One trial involved the comparison of different modes of non-invasive respiratory support as primary respiratory support in preterm infants (Roberts et al., 2016). The other was a pilot RCT investigating the effects of low-dose dexamethasone in preterm infants (The MINIDEX trial, ISRCTN registry number 81191607, <https://doi.org/10.1186/ISRCTN81191607>). The protocols of both trials would have substantially changed the respiratory management of some infants in The VoluVent trial that may have introduced bias into its trial population and its primary outcome.

4.2.10 Strategy for consent procedures regarding co-enrolment

For several months during the recruitment period, this trial was one of four trials into which preterm infants could be co-enrolled. All four trials required parents to be approached within 72 hours of their infants' births. The research team and Consultant Neonatologists met to discuss this as it raised certain challenges. The following four principles were discussed.

1. Multiple concurrent trials should not impose a burden on parents of eligible infants.
2. Only parents should make the decision as to whether they want to receive trial information. Researchers and clinicians should not decide this on behalf of the parents.
3. The four trial protocols were all compatible.
4. Co-enrolment would improve research efficiency and increase the likelihood of recruiting to time and target.

During this meeting a strategy was agreed upon and documented formally as minutes of the meeting. This strategy provided specific details about consent practices whilst the trials were in their concurrent recruitment phases. Consent

for The VoluVent Trial was always sought first as this trial had the earliest deadline in which to seek consent. The aim was to ensure that, wherever possible and appropriate, all parents were offered information about the trials whilst aiming to minimise the burden that this may impose parents.

The minutes of this meeting were compiled and included in the trial master file for The VoluVent Trial and in the relevant files for the other trials.

4.3 Maternal characteristics

Data on baseline maternal and antenatal characteristics that were routinely recorded in the infants' medical records and the national electronic database were collected. The results are shown in Table 4-2. The randomised nature of the study meant that any differences that arose should have been due to chance and should not be analysed for significance. Therefore no statistical analyses were performed on maternal and antenatal characteristics.

There were small differences in the proportions of mothers receiving antenatal steroids between the two groups. Fifty-four mothers (98%) of infants in the VG group received at least one dose of antenatal steroids compared with 49 (85%) mothers in the VCV group. Forty-three mothers (78%) of infants in the VG group received at least two doses of antenatal steroids, compared with 36 (63%) of mothers respectively in the VCV group.

Exposure to antenatal steroids was analysed as a covariate for the primary outcome and is discussed in section 4.11. The trial site's Annual Neonatal Reports published in 2013 and 2014 (Garg et al., 2013; Garg, 2014) state that the antenatal steroid administration rates for women who delivered infants between 24 and 34 weeks' gestation in 2014 were 87% and 83% respectively. Therefore a greater proportion of infants in this trial were exposed to at least one dose of antenatal steroids prior to delivery than the overall population at the trial site.

Characteristics	VG n = 55	VCV n = 57	Total population n = 112
Maternal age, years, mean (SD)	29 (4.8)	28 (5.4)	28 (5)
Maternal ethnicity			
White British, n (%)	49 (89.1)	53 (93)	102 (91.1)
Asian Bangladeshi, n (%)	5 (9.1)	3 (5.3)	8 (7.1)
White, other, n (%)	1 (1.8)	1 (1.7)	2 (1.8)
Multiple pregnancy			
Yes, n (%)	18 (32.7)	22 (38.6)	40 (35.7)
No, n (%)	37 (67.3)	35 (61.4)	72 (64.3)
At least one dose of antenatal steroids received			
Yes, n (%)	54 (98.2)	49 (86)	103 (92)
No, n (%)	1 (1.8)	8 (14)	9 (8)
Doses of antenatal steroids received			
None, n (%)	1 (1.8)	8 (14)	9 (8)
1 dose, n (%)	11 (20)	13 (22.8)	24 (21)
≥2 doses, n (%)	43 (78.2)	36 (63.2)	79 (71)
PPROM before 23 weeks' gestation			
Yes, n (%)	2 (3.6)	1 (1.8)	3 (2.7)
No, n (%)	52 (94.5)	56 (98.2)	108 (96.4)
Missing data, n (%)	1 (1.8)	0 (0)	1 (0.9)
GBS isolated in this pregnancy			
Yes, n (%)	10 (18.2)	12 (21.1)	22 (19.6)
No, n (%)	43 (78.2)	44 (77.2)	87 (77.7)
Missing data, n (%)	2 (3.6)	1 (1.8)	3 (2.7)
Maternal chorioamnionitis			
Yes, n (%)	12 (21.8)	13 (22.8)	25 (22.3)
No, n (%)	38 (69.1)	37 (64.9)	75 (67)
Missing data, n (%)	5 (9.1)	7 (12.3)	12 (10.7)
Maternal fever ≥38 °C			
Yes, n (%)	5 (9.1)	3 (5.3)	8 (7.1)
No, n (%)	41 (74.5)	45 (78.9)	86 (76.8)
Missing data, n (%)	9 (16.4)	9 (15.8)	18 (16.1)
Antenatal antibiotics			
Yes, n (%)	12 (21.8)	17 (29.8)	29 (25.9)
No, n (%)	24 (43.6)	17 (29.8)	41 (36.6)
Missing data, n (%)	19 (34.5)	23 (40.4)	42 (37.5)
Intrapartum antibiotics received >4 hours before delivery			
Yes, n (%)	20 (36.4)	15 (26.3)	35 (31.3)
No, n (%)	29 (52.7)	31 (54.4)	60 (53.6)
Missing data, n (%)	6 (10.9)	11 (19.3)	17 (15.2)

Any positive maternal culture			
Yes, n (%)	26 (47.3)	23 (40.4)	49 (43.8)
No, n (%)	26 (47.3)	32 (56.1)	58 (51.8)
Missing data, n (%)	3 (5.5)	2 (3.5)	5 (4.5)
Antepartum haemorrhage			
Yes, n (%)	15 (27.3)	17 (29.8)	32 (28.6)
No, n (%)	40 (72.7)	38 (66.7)	78 (69.6)
Missing data, n (%)	0 (0)	2 (3.5)	2 (1.8)
Pregnancy-induced hypertension			
Yes, n (%)	2 (3.6)	3 (5.3)	5 (4.5)
No, n (%)	53 (96.4)	52 (91.2)	105 (93.8)
Missing data, n (%)	0 (0)	2 (3.5)	2 (1.8)
Pre-eclampsia			
Yes, n (%)	3 (5.5)	3 (5.3)	6 (5.4)
No, n (%)	52 (94.5)	52 (91.2)	104 (92.9)
Missing data, n (%)	0 (0)	2 (3.5)	2 (1.8)
Eclampsia			
Yes, n (%)	0 (0)	0 (0)	0 (0)
No, n (%)	0 (0)	0 (0)	0 (0)
Maternal diabetes			
Yes, n (%)	2 (3.6)	2 (3.5)	4 (3.6)
No, n (%)	53 (96.4)	55 (96.5)	108 (96.4)

Table 4-2 Baseline maternal and antenatal characteristics

SD, standard deviation; n, number.

Missing data refer to variables for which the information was missing from the infants' notes. Where missing data are not indicated these variables had complete data collection.

4.4 Trial population

The baseline characteristics of the trial population are described in Sections 4.4 to 4.6. As with the maternal data, randomisation meant that any differences that arose should have been due to chance and should not be analysed for significance. Therefore no statistical analyses have been performed on the trial population's baseline characteristics.

4.4.1 Delivery details for all infants

The characteristics of all infants at the time of delivery are summarised in Table 4-3. The mean gestational age was 27.7 weeks' gestation at birth. Similar values were seen when the two intervention groups were compared. The

median birth weight was 1030g for the total population. Similar median weights were seen when the two intervention groups were compared.

In both groups there were more male than female infants (57.1% male and 42.9% female). The difference was slightly greater in the VCV group in which 61.4% were male and 38.6% were female. However the absolute differences in numbers of infants is small.

Table 4-3 demonstrates the following points.

- The majority of infants was born at the trial site.
- Almost two thirds of infants had been exposed to labour before delivery.
- Approximately half were delivered by lower segment caesarian section (LSCS).
- Approximately one third of the infants in the trial were part of a multiple pregnancy at delivery.
- Almost two thirds of infants were intubated in the delivery room meaning that one third received NIV for some time in the delivery room and in the neonatal unit prior to intubation.
- The median age of infants on admission to the unit was 29 minutes (IQR 19.25 – 53 minutes), indicating that most infants received intensive care according to the trial protocol shortly after birth.

Three infants were born unexpectedly at home. These infants were transferred from home to the trial site by ambulance. Given that these infants first received neonatal care at the trial site, they were designated as inborn infants for the purpose of data analysis. These infants were all randomised to the VCV arm of the trial.

Characteristics	VG n = 55	VCV n = 57	Total population n = 112
Completed weeks of gestation at the time of delivery, mean (SD)	27.5 (2.89)	27.8 (2.37)	27.7 (2.63)
Birth weight, g, median (IQR)	1020 (700 – 1530)	1080 (800-1395)	1030 (780-1475)
Small for gestational age Yes, n (%) No, n (%)	11 (20) 44 (80)	10 (17.5) 47 (82.5)	21 (18.8) 91 (81.2)
Gender Male, n (%) Female, n (%)	29 (52.7) 26 (47.3)	35 (61.4) 22 (38.6)	64 (57.1) 48 (42.9)
Born at the trial site Inborn, n (%) Outborn, n (%)	45 (81.8) 10 (18.2)	43 (75.4) 14 (24.6)	88 (78.6) 24 (21.4)
Labour before delivery Yes, n (%) No, n (%)	34 (61.8) 21 (38.2)	37 (64.9) 20 (35.1)	71 (63.4) 41 (36.6)
Born by LSCS Yes, n (%) No, n (%)	24 (43.6) 31 (56.4)	33 (57.9) 24 (42.1)	57 (50.9) 55 (49.1)
Breech presentation Yes, n (%) No, n (%) Missing data, n (%)	20 (36.4) 31 (56.4) 4 (7.3)	20 (35.1) 28 (49.1) 9 (15.8)	40 (35.7) 59 (52.7) 13 (11.6)
Multiple births Yes, n (%) No, n (%)	19 (34.5) 36 (65.5)	21 (36.8) 36 (63.2)	40 (35.7) 72 (64.3)
Intubated in the delivery room Yes, n (%) No, n (%)	34 (61.8) 21 (38.2)	37 (64.9) 20 (35.1)	71 (63.4) 41 (36.6)
Apgar score at five minutes, n, median (IQR) Missing data, n (%)	7 (5.75 – 9) 5 (9.1)	8 (7 – 9) 6 (10.5)	8 (6 – 9) 11 (9.8)
Age on admission to trial site, minutes, median (IQR)	29 (18 – 39)	31 (19.5–67.5)	29 (19.25 – 53)
First recorded admission temperature, °C, mean (SD) Missing data, n (%)	37 (0.85) 1 (1.8)	36.9 (0.71) 4 (7)	37 (0.78) 4 (4.5)

Table 4-3 Delivery details for all infants

SD, standard deviation; g, grams; IQR, interquartile range; n, number; LSCS, lower segment caesarian section; °C, degrees Celsius. Missing data refer to variables for which the information was missing from the infants' notes. Where missing data are not indicated these variables had complete data collection.

4.5 Comparison of the stratified groups according to gestational age

Infants were stratified before randomisation into two groups, those born at <28 weeks of gestation and those born at 28 – 33+6 weeks' of gestation. This stratification was chosen because more mature preterm infants (28 – 33+6 weeks' gestation) are more likely to be ready for extubation earlier than extremely preterm infants (<28 week's gestation). Therefore infants were stratified before randomisation in order to ensure a balance of randomisation across the trial population.

The stratification achieved a good balance of randomisation across the two sub-groups. There were 54 infants in the sub-group of infants born at <28 weeks' gestation, 27 of whom were randomised to VG and 27 of whom were randomised to VCV. There were 58 infants in the 28 – 33+6 weeks' gestation sub-group, 28 of whom were randomised to VG and 30 of whom were randomised to VCV.

The characteristics of the two sub-groups are shown in Table 4-4 and Table 4-5. These prognostic characteristics were well balanced between the two arms of the trial in both sub-groups. These characteristics can affect a preterm infant's requirement for mechanical ventilation therefore the balance indicates effective randomisation. The absolute numbers of infants in these sub-groups are small but in a larger trial the effect of some of these characteristics could be investigated using regression analyses.

4.5.1 Infants born at <28 weeks' gestation

In infants born at <28 weeks' gestation, the mean (SD) gestational age was 25.4 (1.29) weeks' gestation. The median (IQR) birth weight was 775g (657 – 916 g).

Table 4-4 demonstrates the following points.

- Just over half of the infants were male (53.7%). The proportion of male infants in the VCV group was slightly greater (59.3%) although the absolute numbers are small.
- A greater proportion of infants in the VG group (88.9%) was born at the trial site compared with the VCV group (66.7%). However, the absolute numbers are small.

- Approximately three quarters of infants had been exposed to labour before delivery.
- The proportion of infants born by LSCS was greater in the VCV group (48.1%) compared with the VG group (22.1%) although the absolute numbers are small.
- The majority of infants (88.9%) was intubated in the delivery room. Similar proportions were seen in the VCV and the VG groups meaning that most infants received mechanical ventilation within the first few minutes of life.

Characteristics	VG N = 27	VCV N = 27	Total population N = 54
Completed weeks of gestation at the time of delivery, mean (SD)	25 (1.43)	25.7 (1.07)	25.4 (1.29)
Birth weight, g, median (IQR)	700 (650 – 915)	800 (680 – 920)	775 (657 – 916)
Small for gestational age			
Yes, n (%)	7 (25.9)	6 (22.2)	13 (24.1)
No, n (%)	20 (74.1)	21 (77.8)	41 (75.9)
Gender			
Male, n (%)	13 (48.1)	16 (59.3)	29 (53.7)
Female, n (%)	14 (51.9)	11 (40.7)	25 (46.3)
Born at the trial site			
Inborn, n (%)	24 (88.9)	18 (66.7)	42 (77.8)
Outborn, n (%)	3 (11.1)	9 (33.3)	12 (22.2)
Labour before delivery			
Yes, n (%)	21 (77.8)	20 (74.1)	41 (75.9)
No, n (%)	6 (22.2)	7 (25.9)	13 (24.1)
Born by LSCS			
Yes, n (%)	6 (22.2)	13 (48.1)	19 (35.2)
No, n (%)	21 (77.8)	14 (51.9)	35 (64.8)
Breech presentation			
Yes, n (%)	11 (40.1)	11 (40.7)	22 (40.7)
No, n (%)	15 (55.6)	12 (44.4)	27 (50)
Missing data, n (%)	1 (3.7)	4 (14.8)	5 (9.3)
Multiple births			
Yes, n (%)	8 (39.6)	9 (33.3)	17 (31.5)
No, n (%)	19 (70.4)	18 (66.7)	37 (68.5)
Intubated in the delivery room			
Yes, n (%)	23 (85.2)	25 (92.6)	48 (88.9)
No, n (%)	4 (14.8)	2 (7.4)	6 (11.1)
Apgar score at five minutes, median (IQR)	7 (5 – 8)	7 (5 – 9)	7 (5 – 8)
Missing data, n (%)	2 (7.4)	4 (14.8)	6 (11.1)
Age on admission to trial site, minutes, median (IQR)	25 (18 – 37)	29 (22 – 198)	28.5 (19.5 – 43.5)
First recorded admission temperature, °C, mean (SD)	36.9 (1.01)	36.9 (0.82)	36.9 (0.92)
Missing data, n (%)	1 (3.7)	3 (11.1)	4 (7.4)

Table 4-4 Delivery details of infants born at <28 weeks' gestation

SD, standard deviation; g, grams; IQR, interquartile range; n, number; LSCS, lower segment caesarian section; °C, degrees Celsius. Missing data refer to variables for which the information was missing from the infants' notes. Where missing data are not indicated these variables had complete data collection.

4.5.2 Infants born at 28 – 33+6 weeks' gestation

In infants born at 28 – 33+6 weeks' gestation, the mean (SD) gestational age was 30 (1.51) weeks' gestation. The median (IQR) birth weight was 1415g (1164 – 1703g). When the two groups were compared the median birth weight in the VG group was slightly higher than in the VCV group (1525g and 1355g respectively).

Table 4-5 demonstrates the following points.

- Sixty per cent of infants were male. Similar proportions were seen in both the VCV and VG groups
- Approximately three quarters of infants were born at the trial site and this proportion was similar in the VCV and VG groups.
- When compared with the total population, and with the infants born at <28 weeks' gestation, fewer infants in this group had been exposed to labour before delivery (51.7%) and a larger proportion (65.5%) were born by LSCS.
- Only 39.7% of infants born in this gestational age group were intubated in the delivery room, meaning that most of these infants received NIV initially before receiving mechanical ventilation later on in the neonatal unit.

Given the increased use of NIV as primary respiratory support for preterm infants (Schmölzer et al., 2013) the finding that most infants in this group received NIV initially was not surprising.

Characteristics	VG N = 28	VCV N = 30	Total population N = 58
Completed weeks of gestation at the time of delivery, mean (SD)	30 (1.5)	30 (1.5)	30 (1.51)
Birth weight, g, median (IQR)	1525 (1116–1787)	1355 1167–1655)	1415 (1164-1703)
Small for gestational age			
Yes, n (%)	4 (14.3)	4 (13.3)	8 (13.8)
No, n (%)	24 (85.7)	26 (86.7)	50 (86.2)
Gender			
Male, n (%)	16 (57)	19 (63)	35 (60)
Female, n (%)	12 (43)	11 (37)	23 (40)
Born at the trial site			
Inborn, n (%)	21 (75)	22 (73.3)	43 (74.1)
Outborn, n (%)	7 (25)	8 (26.7)	15 (25.9)
Labour before delivery			
Yes, n (%)	13 (46.4)	17 (56.7)	30 (51.7)
No, n (%)	15 (53.6)	13 (43.3)	28 (48.3)
Born by LSCS			
Yes, n (%)	18 (64.3)	20 (66.7)	38 (65.5)
No, n (%)	10 (35.7)	10 (33.3)	20 (34.5)
Breech presentation,			
Yes, n (%)	9 (32.1)	9 (30)	18 (31)
No, n (%)	16 (57.1)	16 (53.3)	32 (55.2)
Missing data, n (%)	3 (10.7)	5 (16.7)	8 (13.8)
Multiple births			
Yes, n (%)	11 (39.3)	12 (40)	23 (39.7)
No, n (%)	17 (60.7)	18 (60)	35 (60.3)
Intubated in the delivery room			
Yes, n (%)	11 (39.3)	12 (40)	23 (39.7)
No, n (%)	17 (60.7)	18 (60)	35 (60.3)
Apgar score at five minutes, median (IQR)	8 (6 – 9)	8 (7 – 9)	8 (7 – 9)
Missing data, n (%)	3 (10.7)	2 (6.7)	5 (8.6)
Age on admission to trial site, minutes, median (IQR)	30.5 (21.3 – 270.5)	34.5 (16.8 – 56.5)	31 (18.5–56.5)
First recorded admission temperature, °C, median (IQR)	37 (36.6 – 37.4)	37 (36.6 – 37.4)	37 (36.6–37.4)
Missing data, n (%)	0 (0)	1 (3.3)	1 (1.7)

Table 4-5 Delivery details of infants born at 28 – 33-6 weeks' gestation

SD, standard deviation; g, grams; IQR, interquartile range; n, number; LSCS, lower segment caesarian segment; °C, degrees Celsius. Missing data refer to variables for which the information was missing from the infants' notes.

Variables without missing data had complete data collection.

4.6 Comparison of infants born at the trial site with those born in other hospitals

Eighty-eight infants (79%) were recorded as inborn infants. These include three infants who were born at home and brought by ambulance to the trial site.

These three infants first received hospital care at the trial site. Therefore they were recorded as inborn infants for the purpose of data collection and analysis. Twenty-four infants were born at other hospitals and transferred to the trial site for intensive care.

Randomisation was balanced in the group of inborn infants with 45 infants randomised to VG and 43 randomised to VCV.

Table 4-6 demonstrates the following points.

- Equal proportions of inborn infants received non-invasive ventilation (NIV) prior to trial entry. The median duration of NIV prior to trial entry was longer in the VCV group than in the VG group.
- Inborn infants in the VCV group did not receive any other modes of ventilation prior to trial entry because VCV was the standard mode of ventilation used in the trial unit. Any infant receiving ventilation before randomisation was ventilated using VCV. Therefore these infants did not require a change of ventilation if they were then randomised to VCV.
- Thirteen (29%) of infants in the VG group received a different mode of ventilation prior to randomisation and trial entry. Ten infants received VCV before randomisation to VG. Four of these had been enrolled before the introduction of deferred consent. They were managed according to the protocol which stated that they should receive VCV prior to randomisation. Two infants received pressure-limited modes of ventilation. One infant initially received HFOV but was changed to VG at less than 24 hours of age.

Therefore, the respiratory management of infants before enrolment was similar between groups. The only important difference between groups was that some infants in the VG group had received a difference mode of ventilation before randomisation. This was to be expected given the reasons stated above.

Characteristics	VG n = 45	VCV n = 43	Total population n = 88
Non-invasive ventilation used before intubation, n (%)	9 (20)	9 (21)	18 (21)
Duration of non-invasive ventilation before intubation, minutes, median (IQR)	202 (140 – 585)	375 (156 – 1055)	233 (148-710)
Age at intubation, minutes, median (IQR)	12 (8 – 73)	12.5 (7 – 55)	12 (7 – 62)
Doses of surfactant received before starting trial mode, n (%)			
No doses	0 (0)	4 (9.3)	4 (4.5)
One dose	45 (100)	39 (90.7)	84 (95.5)
Doses of surfactant received in total, n (%)			
One dose	23 (51.1)	22 (51.2)	45 (51.1)
Two doses	17 (37.8)	17 (39.5)	34 (38.6)
Three doses	5 (11.1)	4 (9.3)	9 (10.3)
Mechanically ventilated before starting trial mode, n (%)	13 (29)	0 (0)	13 (15)
Duration of mechanical ventilation prior to starting trial mode, minutes, median (IQR)	195 (66 – 525)	N/A	195 (66 – 525)
Age when starting trial mode, minutes, median (IQR)	50 (29 – 202)	40 (25 – 75)	44 (27 – 136)

Table 4-6 Respiratory management received by inborn infants before enrolment
n, number; IQR, interquartile range

Table 4-7 shows the respiratory management of outborn infants before enrolment. This sub-group was very small, consisting of only 24 infants. Ten infants were randomised to VG and 14 were randomised to VCV.

All outborn infants received mechanical ventilation prior to trial entry. This may have affected the results of their outcome measures. For this reason a sub-group analysis of the primary outcome was undertaken excluding outborn infants as planned *a priori* in the SAP (see Appendix 9.3). Although there was an imbalance between groups in the numbers of infants receiving NIV at the referring hospital, the absolute numbers are very small. The median duration of time spent on NIV prior to receiving ventilation was similar between the two groups.

Characteristics	VG n = 10	VCV n = 14	Total population n = 24
Level 1 referring unit, n (%)	8 (80)	10 (71)	18 (75)
Non-invasive ventilation used at referring hospital, n (%)	8 (80)	4 (29)	12 (50)
Duration of non-invasive ventilation at referring hospital, minutes, median (IQR)	205 (165 – 285)	200 (153 – 494)	205 (165 – 285)
Mechanically ventilated at referring hospital, n (%)	10 (100)	14 (100)	24 (100)
Age at intubation, minutes, median (IQR)	185 (81 – 317)	36 (4.5 – 182)	109 (5 – 222)
Doses of surfactant received at referring hospital, n (%)			
No doses	0 (0)	0 (0)	0 (0)
One dose	8 (80)	9 (64.3)	17 (70.8)
Two doses	2 (20)	4 (28.6)	6 (25)
Three doses	0 (0)	1 (7.1)	1 (4.2)
Doses of surfactant received in total, n (%)			
One dose	7 (70)	7 (50)	14 (58.3)
Two doses	3 (30)	4 (28.6)	7 (29.2)
Three doses	0 (0)	3 (21.4)	3 (12.5)
Duration of ventilation prior to starting trial mode of ventilation, minutes, mean (SD)	186 (82)	372 (146)	295 (153)
Age on arrival at trial site, minutes, median (IQR)	375 (326 – 442)	395 (346 – 577)	378 (341 – 498)
Age when starting trial mode, minutes, median (IQR)	375 (329 – 449)	421 (346 – 556)	393 (341 – 499)

Table 4-7 Respiratory management of outborn infants before enrolment
n, number; IQR, interquartile range; SD, standard deviation

Table 4-8 shows a comparison between inborn and outborn infants in their characteristics and respiratory management before enrolment. They were similar in mean gestational ages and in birth weights. A larger proportion of outborn infants had received NIV prior to starting mechanical ventilation compared with inborn infants. Outborn infants were much older by the time they started the trial mode of ventilation (median age 393 minutes, IQR 341 – 499 minutes) compared with the inborn infants (median age 44 minutes, IQR 27 –

136 minutes). This is not surprising and reflects the fact that outborn infants required transfer to the trial unit for intensive care.

Characteristics	Inborn infants n = 88	Outborn infants n = 24
Completed weeks of gestation at the time of delivery, mean (SD)	28 (2.7)	28 (2.3)
Birth weight, g, median (IQR)	1030 (725 – 1465)	1170 (850 – 1490)
Gender:		
Male, n (%)	48 (57)	16 (59)
Female, n (%)	37 (43)	11 (41)
Singleton, n (%)	55 (65)	17 (63)
Received non-invasive ventilation before intubation, n (%)	18 (21)	12 (50)
Duration of non-invasive ventilation before intubation, minutes, median (IQR)	233 (148 – 710)	205 (165 – 285)
Age at intubation, minutes, median (IQR)	12 (7 – 62)	109 (5 – 222)
Doses of surfactant received in total, n (%)		
One dose	45 (51.1)	14 (58.3)
Two doses	34 (38.6)	7 (29.2)
Three doses	9 (10.2)	3 (12.5)
Duration of ventilation prior to starting trial mode of ventilation, minutes, median (IQR)	195 (66 – 525)	275 (197 – 374)
Age at start of trial mode, minutes, median (IQR)	44 (27 – 136)	393 (341 – 499)

Table 4-8 Characteristics of inborn infants compared to outborn infants
SD, standard deviation; g, grams; IQR, interquartile range; n, number

4.7 Assessment of radiological features of RDS

The case record forms had been designed to collect data on the radiographic appearances of enrolled infants. A Consultant Paediatric Radiologist, who was blinded to allocation, initially reviewed the first chest x-rays of enrolled infants to ascribe a standardised score to the appearances of RDS. It was intended that this score would form part of the comparison of respiratory status between the two groups of infants.

However, it quickly became apparent that this information could not be collected consistently or accurately. Many infants had been intubated and given surfactant before their first chest x-ray, meaning that the radiological features of RDS were altered or completely absent. The x-rays of some outborn infants were not transferred from the local hospital to the trial site's radiology computer system, despite repeated requests by the Principal Investigator. These x-rays could not be analysed. Therefore data collection of chest x-ray appearances was discontinued.

4.8 Comparison of respiratory parameters and ventilatory requirements after starting the trial mode

Table 4-9 shows a comparison of the respiratory parameters and ventilatory requirements of all infants randomised to VG and to VCV. These data were collected from the nursing observation charts in the infants' medical records. In accordance with routine clinical practice they were recorded by the nurses as soon as possible after starting the trial mode.

In both groups, the ventilatory support after starting the trial modes was similar. The mean and peak airway pressures, the expired tidal volumes and the FiO_2 were low in both groups. The median lung compliance for the total population was 0.34 mls/cmH₂O/kg with similar values seen in both intervention groups. This is consistent with the reference value of 0.35 mls/cmH₂O/kg (Van Kaam et al., 2015) for infants born at 27 – 28 weeks' gestation who had received surfactant for RDS in the first three days of life. This is also consistent with the median gestational age of the trial population (28 weeks' gestation).

Therefore, these parameters demonstrate the following points.

- The trial population had low ventilatory and oxygen requirements at the point of trial entry. This is common for preterm infants who have just received surfactant.
- Their respiratory parameters were within acceptable ranges for ventilated preterm infants.

Parameters	VG n = 55	VCV n = 57	Total population n = 112
Mean airway pressure, cm H ₂ O, median (IQR)	9 (8 – 11)	9 8 – 10)	9 (8 – 10)
Peak inspiratory pressure, cm H ₂ O, mean (SD)	21 (6.8)	19 (4.1)	20 (5.6)
Expired tidal volume, mls/kg, median (IQR)	4.4 (4 – 4.7)	4.3 (3.7 – 5.4)	4.4 (3.9 – 5)
Minute volume, mls/minute, median (IQR)	280 (185 – 390)	295 (190 – 400)	290 (190 – 395)
Fraction of inspired oxygen, median (IQR)	0.23 (0.21 – 0.32)	0.23 (0.21 – 0.39)	0.23 (0.21 – 0.35)
Lung compliance, ml/cmH ₂ O/kg, median (IQR)	0.33 (0.23 – 0.51)	0.38 (0.2 – 0.49)	0.34 (0.21 – 0.49)

Table 4-9 Comparison of respiratory and ventilation parameters at trial entry

IQR, interquartile range; SD, standard deviation; n, number; mls, millilitres; kg, kilogram

4.9 Respiratory support and adjunctive weaning therapies received before and during the trial

This sub-section discusses the respiratory support and adjunctive therapies received by enrolled infants before and during the trial. Much of these are descriptive data regarding compliance with the trial protocol. However, data from outborn infants are included and, before arriving at the trial site, they did not receive management according to the protocol. Table 4-10 presents a summary of these data.

4.9.1 Presentation of data on infants enrolled before the introduction of deferred consent

Before the introduction of deferred consent six infants were enrolled. They were randomised after consent had been obtained. They had all received VCV before randomisation. During that time their management whilst on VCV was in accordance with the trial protocol on ventilation of infants allocated to VCV.

Four of these infants were randomised to VCV. Therefore, randomisation did not lead to a change in their ventilatory management. In Table 4-10 they are

included in the numbers of infants who received ventilation before randomisation. The duration of time that they received VCV before randomisation is included in the data on the 'duration of ventilation before randomisation'. However, because they were managed according to the trial protocol before randomisation, this duration of time is also included in their primary outcome data (Section 4.10).

Two infants were randomised to VG. They had received VCV before randomisation. The duration of time that they received VCV before randomisation is included in the data on the 'duration of ventilation before randomisation'.

4.9.2 Infants receiving mechanical ventilation before enrolment

Twenty-three (42%) infants in the VG group received a different form of mechanical ventilation before trial entry compared with 16 (28%) of infants in the VCV group. This reflects the fact that some infants in the VG group initially received VCV as part of standard unit practice before randomisation to VG.

4.9.3 Infants receiving only the trial modes of ventilation

The trial protocol stated that infants should receive their randomised mode of ventilation with no cross-over between modes. They could receive high frequency oscillatory ventilation (HFOV) if their conditions deteriorated whilst on their trial mode.

- There was no cross-over between modes during the trial.
- The majority of infants (87%) received only their randomised mode of ventilation, excluding the use of HFOV also.
- Nine infants (8%) received HFOV prior to reaching the primary outcome as part of the pragmatic trial protocol. The results of these infants were analysed on an intention-to-treat basis.

This demonstrates excellent compliance with these elements of the protocol.

4.9.4 Extubation of infants before reaching the 'success' criteria

There were three reasons for extubation of infants before reaching the 'success' criteria. These included

- planned extubation due to hypocarbia,
- planned extubation to avoid prolonged ventilation,
- unplanned but successful extubation.

These events were recorded as part of a process evaluation of the trial. They were accepted by the research team as part of ensuring safety of the participants whilst maintaining feasibility of the protocol. If these infants remained extubated for at least 24 hours they were recorded as having met the primary outcome. The time of extubation was used instead of the 'success' criteria.

4.9.4.1 Planned extubation due to hypocarbia

This was undertaken at the decision of the treating clinician in infants who were hypocarbic despite weaning of ventilation. This was done in order to prevent further hypocarbia which is associated with cause brain injury in preterm infants (Erickson et al., 2002).

Three infants were extubated before reaching the 'success' criteria due to hypocarbia. Two were in the VCV group. One infant was extubated one hour before the SBT was due. The second infant had a MAP of 7-8 cmH₂O but not consistently <8cmH₂O for six consecutive hours. That infant had a SBT due to hypocarbia, despite the other 'success' criteria not being met. The SBT was successful and the infant was extubated. The third infant was in the VG group and was extubated three hours before the SBT was due.

4.9.4.2 Planned extubation to prevent prolonged ventilation

Seven infants were ventilated for prolonged periods. When their ventilation was able to be weaned, these infants reached a point whereby they appeared ready for extubation but were not generating mean airway pressures that were consistently <8cmH₂O. In order to prevent further prolonged ventilation that would not provide benefit to these infants, the treating Consultant Neonatologist made the decision to extubate these infants despite the fact that they had not reached the 'success' criteria. This was accepted by the research team as part of ensuring safety of the participants. Two of the seven infants were in the VG group and five were in the VCV group.

4.9.4.3 Unplanned but successful extubation

Six infants had unplanned but successful extubations, four in the VCV group and two in the VG group. These extubations occurred before reaching the 'success' criteria. These infants were assessed as having good respiratory drive and the treating clinicians decided to support them with CPAP rather than reintubate them just for the purpose of the trial.

4.9.5 Delay in performing the spontaneous breathing test

Due to the busy and unpredictable nature of a neonatal unit, some of the SBTs were not performed immediately. If an SBT was delayed by more than one hour it was recorded as being delayed. The number of infants affected by a delayed SBT, and the reasons for delayed SBTs, were recorded as part of a process evaluation in assessing the feasibility of the trial. In most infants, the delay was due to clinical emergencies or priorities involving other infants in the unit. Delays that were due to protocol misinterpretation or oversight were discussed with clinical team members to aim to ensure that they did not occur again.

In 23 infants the SBT was delayed but was subsequently successful when it was undertaken. Eleven infants were in the VG group. The median (IQR) delay in this group was 108 (80 – 168) minutes. Twelve infants were in the VCV group. The median (IQR) delay in this group was 114 (79 – 210) minutes. Therefore the difference in the median delays between groups was six minutes.

These data demonstrate that the duration of delays, and the numbers of infants affected by them, were comparable between groups. The subsequent effects on the primary outcome results were balanced between groups.

4.9.6 Spontaneous breathing test performed early

In one infant, the SBT was performed one hour early in error. This infant was outborn and received ventilation during transfer from the birth hospital to the trial site. The infant was randomised to VG on arrival at the trial site. Over the next five hours the infant had a MAP <8 cmH₂O and FiO₂ ≤0.35 and the SBT was performed early in error. The infant was then extubated successfully. That infant's primary outcome is recorded as five hours.

4.9.7 Use of volume SIMV

As part of the trial protocol infants in the VCV group could receive volume synchronised intermittent mandatory ventilation (SIMV) with pressure support ventilation (PSV) as part of the weaning process.

Twenty-three infants (40%) in the VCV group received volume SIMV with PSV before the 'success' criteria were reached. They spent a median of 12 hours (IQR 10 – 52 hours) on VCV before changing to SIMV plus PSV. They then received a median of four hours (3 – 12 hours) on SIMV plus PSV before reaching the 'success' criteria.

Another six infants received volume SIMV after the primary outcome had been reached and before the infants were extubated. Twenty-eight infants (49%) did not receive volume SIMV with PSV at all. In these infants, ventilation was weaned using VCV alone.

4.9.8 Infants receiving other modes of ventilation

Before reaching the primary outcome, four infants received a mode of ventilation outwith the trial protocol. These infants all received pressure-limited ventilation as part of a clinical decision made at the time by the treating neonatologist due to concerns about the infant's condition. Data from these infants were analysed on an intention-to-treat basis according to the groups to which they were randomised.

A further four infants received a pressure mode of ventilation whilst still in the trial but after they had reached the primary outcome. In three of these four cases this was specifically due to a clinical decision made by the treating neonatologist. In the fourth case, this was due to an oversight by a member of the clinical team and their trial mode was restarted after 45 minutes.

Therefore the number of protocol deviations regarding mode of ventilation was very low. This demonstrates very good compliance with the protocol in this regard. It shows that implementation of a protocol that excludes pressure-limited modes of ventilation is feasible in a busy tertiary NICU.

4.9.9 Infants receiving pressure-limited ventilation for PDA surgery

Nine infants received surgery for ligation of a patent ductus arteriosus (PDA). Six of these infants underwent this surgery before reaching the 'success' criteria. These infants had to be transferred to the regional cardiothoracic centre for surgery. All of these infants were ventilated at all times during transfer between the two sites and during surgery. During transfer they received pressure-limited ventilation using either a Globe-Trotter™ (Draeger) transport ventilator or a ProPaq (Welch Allyn) ventilator. During surgery they received pressure-limited ventilation using a Primus® (Draeger) ventilator.

Of the six infants who underwent PDA ligation surgery before reaching the 'success' criteria, two were in the VCV group and four were in the VG group. The mean (SD) duration of time spent on pressure-limited ventilation during transfer and surgery was 9.75 (1.7) hours in the VG group. The duration of time for both infants in the VCV group was nine hours each.

These data were analysed on an intention-to-treat basis as pre-specified in the SAP. These periods of ventilation did not represent a protocol deviation. Therefore they are not included in the data showing the numbers of infants receiving pressure-limited ventilation at other times.

4.9.10 Adjunctive therapies to facilitate extubation

The therapies used to facilitate extubation were

- caffeine citrate,
- postnatal corticosteroid administration,
- surgical ligation of a PDA.

The protocol stated that all infants should receive caffeine citrate before reaching the 'success' criteria. Caffeine citrate is used as part of standard practice within the unit to increase the chance of successful extubation (Henderson-Smart D., 2010).

Criteria for the use of postnatal corticosteroids or PDA ligation were not specified in the protocol. The treating Consultant Neonatologists made decisions on an individual case basis to give these therapies to infants whose ventilation was difficult to wean. As they could have affected the primary

outcome, the SAP specified that these therapies would be analysed as possible covariates using Cox proportional regression analyses (see Section 4.11).

Treatment received before and during the trial	VG n = 55	VCV n = 57	Total population n = 112
Received non-invasive ventilation before randomisation, n (%)	17 (31)	13 (23)	30 (27)
Duration of non-invasive ventilation before randomisation, minutes, median (IQR)	204* (158 – 454)	240 (165 – 724)	215* (160 – 549)
Received mechanical ventilation before randomisation, n (%)	23 (42)	16 (28)	39 (35)
Duration of mechanical ventilation before randomisation, minutes, median (IQR)	193 (70 – 285)	358 (275 – 505)	262 (165 – 404)
Received trial intervention only after randomisation and before reaching primary outcome, n (%)	45 (82)	52 (91)	97 (87)
Received HFOV as part of trial protocol before reaching primary outcome or before the data were censored, n (%)	5 (9)	4 (7)	9 (8)
Duration of time on trial mode of ventilation before changing to HFOV, hours, median (IQR)	86 (9 – 507)	38.5 (11 – 295)	39 (10 – 324)
Duration of time on HFOV before primary outcome or before data were censored, hours, median (IQR)	13 (2.8 – 67)	49 (39 – 247)	36 (9 – 82)
Received HFOV as part of trial protocol at any time, n (%)	7 (13)	6 (11)	13 (12)
Received pressure-limited ventilation after enrolment into trial and before reaching the primary outcome, n (%)	2 (4)	2 (4)	4 (4)
Received pressure-limited ventilation after enrolment into trial but after reaching the primary outcome, n (%)	0 (0)	4 (7)	4 (4)
Did not reach 'success' criteria (data censored), n (%)			
Died	3 (5)	1 (2)	4 (4)
Transferred to another hospital	3 (5)	2 (4)	5 (4)
Total (died or transferred)	6 (11)	3 (5)	9 (8)
Received more than one period of ventilation, n (%)			
At least two periods	12 (22)	13 (23)	25 (22)
Two periods	8 (15)	10 (18)	18 (16)
Three periods	4 (7)	2 (4)	6 (5)
Four periods	0 (0)	1 (2)	1 (1)

Received postnatal steroid therapy to facilitate extubation before reaching primary outcome, n (%)	4 (7)	2 (4)	6 (5)
Received postnatal steroid therapy to facilitate extubation at any time, n (%)	8 (15)	7 (12)	15 (13)
Received surgical treatment of PDA before reaching primary outcome, n (%)	4 (7)	2 (4)	6 (5)

Table 4-10 Summary of respiratory support and adjunctive weaning therapies received by trial infants

n, number; IQR, interquartile range; HFOV, high frequency oscillatory ventilation; PDA, patent ductus arteriosus

*Data missing for one infant

4.9.11 Summary of respiratory support and adjunctive therapies

These data demonstrate that the trial protocol was implemented successfully with very few deviations. Eighty-seven per cent of infants received only the mode of ventilation to which they were randomised and very few required HFOV as part of the trial protocol. This represents very good protocol compliance. Very few infants received pressure-limited ventilation outwith the protocol and very few required additional therapies to facilitate extubation.

This demonstrates that the protocol was feasible and sufficiently pragmatic for use within a neonatal intensive care setting.

4.10 Primary outcome results

4.10.1 Presentation of data

The primary outcome results are presented here. The reasons for censoring data are described first. Summaries of the primary outcome results for the whole population and for the pre-specified sub-groups are then presented.

The data are presented as the duration of time in hours from starting the trial mode until reaching the 'success' criteria. The data were initially collected and recorded in minutes for precision. They were not normally distributed, with most infants reaching the 'success' criteria within 48 hours. Therefore, in order to analyse and present the data in a relevant format they were converted into hours before analysis and analysed as integers. Numbers with a proportion of an hour that was <0.5 of an hour were rounded down to the nearest integer. Numbers with a proportion of an hour that was ≥ 0.5 of an hour were rounded up to the nearest integer.

For example, if, after conversion from minutes to hours, an infant's primary outcome result was 18.3 hours, it was rounded down to 18 hours before analysis. If the result was 18.6 hours, it was rounded up to 19 hours before analysis.

4.10.2 Censored data

Nine infants did not reach the primary outcome because they died or were transferred to another hospital before reaching the primary outcome. The primary outcome data for these infants are therefore censored as part of the Kaplan Meier time-to-event analyses.

Six infants in the VG group had censored data, of which three died and three were transferred to another hospital to receive further intensive care. Two of the three infants were transferred for surgery. The third was transferred to the surgical centre whilst ventilated in order to be closer to the family home.

Three infants in the VCV group had censored data. Two died prior to reaching the primary outcome. One was transferred to the surgical centre for surgery.

4.10.3 Median time to 'success' criteria

Table 4-11 shows the median times to 'success' criteria for the whole trial population and for the pre-specified sub-groups. The results are presented according to the infants' randomised modes. As this trial was not powered to show statistical significance the results have been presented as medians and hazard ratios (HRs) with CIs.

The HRs were calculated using the VCV group as the reference group and the VG group as the comparator group. In summary, HRs <1 favour the VCV group and HRs >1 favour the VG group. The closer a HR is to 1, the smaller the difference in the hazard rate (number of infants reaching the 'success' criteria at any time) between the two groups. The CIs reflect the degree of certainty around each HR. The wider the CI, the greater the degree of uncertainty and vice versa (Parmar et al., 1995).

The results for each individual group or sub-group will be discussed in Sections 4.10.5 to 4.10.7. The apparent discrepancy in favourable results between the median data and the HRs will be discussed in more detail in those sections.

Group or sub-group	Median time to success criteria, hours, (95% CI)		Hazard ratio (95% CI)
	VG	VCV	
All infants n = 112	23 (10.78 – 35.22)	36 (18.0 – 53.97)	0.93 (0.63 – 1.37)
Infants <28 weeks' gestation n = 54	102 (90.00 – 204.69)	79 (0.00 – 177.71)	0.76 (0.42 – 1.37)
Infants 28 - 33+6 weeks' gestation n = 58	19 (16.48 – 21.52)	24 (11.92 – 36.08)	1.6 (0.92 – 2.82)
Inborn infants n = 88	32 (13.46 – 50.54)	25 (12.6 – 37.4)	0.75 (0.47 – 1.19)

Table 4-11 Comparison of median time to success criteria

CI, confidence interval; n, number.

4.10.4 Comparison of response rates using early phase trial methodology

As explained in the SAP (version 11, dated 8th July 2016, Appendix 9.3) a review of the sample size calculation after the trial oversight review revealed

that a log-rank statistical comparison of the time-to-event analyses would be underpowered. Therefore, an alternative early phase trial methodology approach, amenable to pilot trials, was used to compare response rates between the two groups (Jung, 2008). This was pre-specified in Sections 6.2 and 6.3 of the SAP. A ‘response’ was defined as an infant reaching the ‘success’ criteria. The response rates were the numbers of infants reaching the ‘success’ criteria in the VCV and VG groups.

Time since starting trial mode (hours)	Response rate (number of infants reaching ‘success’ criteria)	
	VG n = 55	VCV n = 57
48	34 (62%)	33 (58%)

Table 4-12 Comparison of response rates using early phase trials methodology (Jung, 2008)

Table 4-12 shows that, 48 hours after starting the trial mode, there was no difference in response rate between the two groups. The SAP had stated that a 15% difference between groups would be considered potentially significant and that this would be one of the thresholds used to proceed to a larger trial. However, this difference as based on an expected response rate at 48 hours of 80% in the VCV group and 95% in the VG group. As shown in Table 4-12, the response rates were lower at this time point in both groups. Therefore, in this trial, fewer infants than expected had reached the ‘success’ criteria by 48 hours.

The decision to use 48 hours as the time point at which to measure response rates was based on previous trial data from the same trial site reported by Singh et al. (Singh et al., 2006). That trial compared VCV with PLV and used similar but not identical ‘success’ criteria. Those factors may explain the differences between that trial and this one in response rates seen at 48 hours in this trial. This is discussed further in Section 7.5.1 of Chapter 8 Discussion.

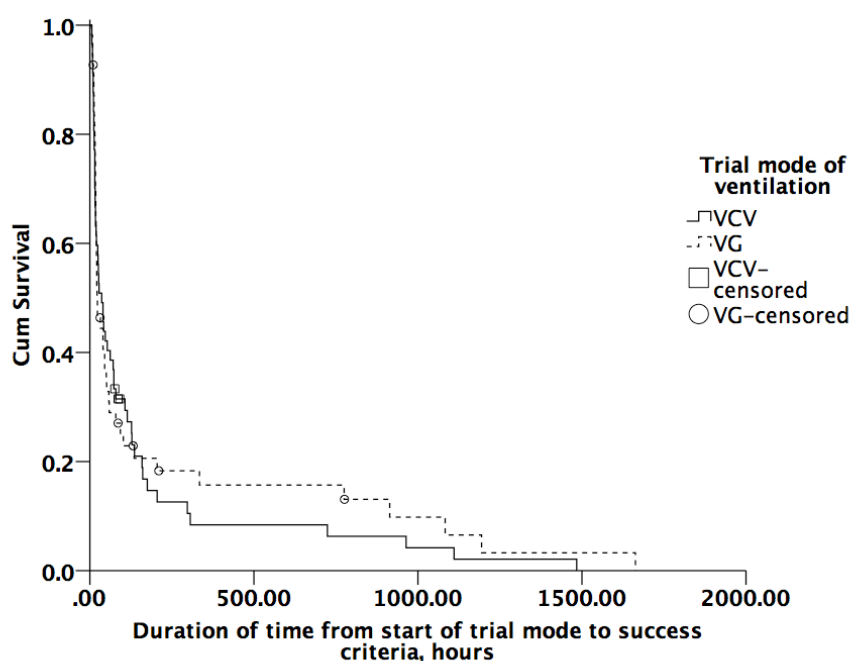
Table 4-13 and Figure 4-4 show that the rates at which infants reached the ‘success’ criteria were highest in the first 24 hours. When using this time point for comparison of response rates, the difference between groups is greater (11%). Therefore use of this time point might be a more appropriate end-point in future research.

Time since starting trial mode (hours)	Response rate (number of infants reaching 'success' criteria)	
	VG n = 55	VCV n = 57
24	29 (53%)	23 (40%)
48	34 (62%)	33 (58%)
72	38 (69%)	36 (63%)
96	40 (73%)	39 (68%)

Table 4-13 Rates at which infants reached the 'success' criteria in the first 96 hours.

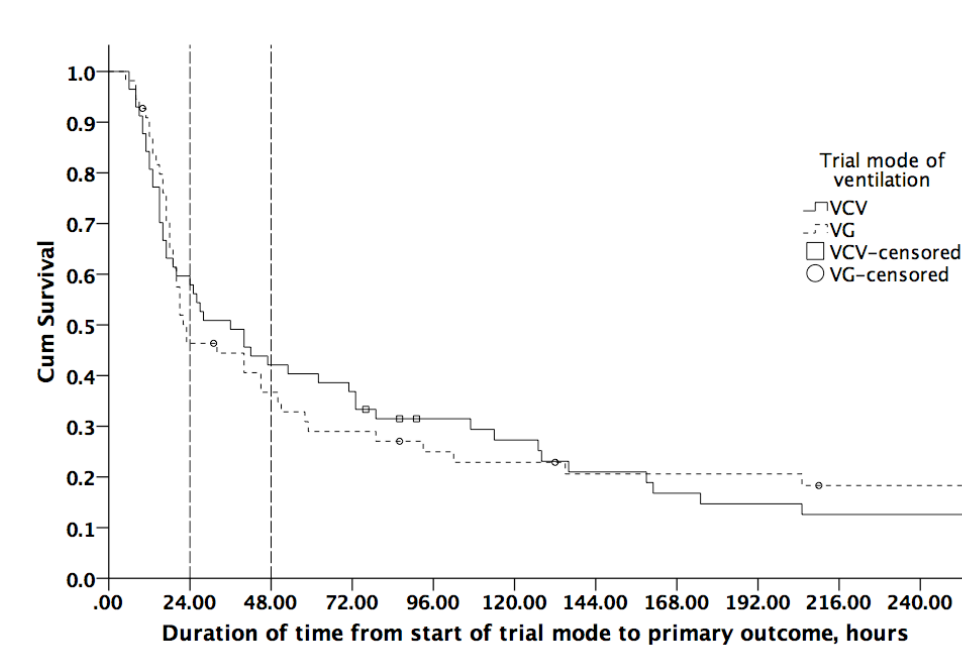
4.10.5 Primary outcome results for the whole trial population

Figure 4-3 and Figure 4-4 show the Kaplan-Meier curves for the time-to-event analyses for the whole trial population. Both curves represent the same data and analysis. Figure 4-3 shows the entire curves. Figure 4-4 focuses on the first 240 hours. In doing so, Figure 4-4 demonstrates more clearly that the rates at which infants reached the 'success' criteria were highest within the first few days, and particularly within the first 24 hours.



Time (hours)	250	500	750	1000	1250	1500
Number remaining (VCV)	6	4	3	2	1	0
Number remaining (VG)	7	6	6	3	1	1

Figure 4-3 Kaplan-Meier curves of time to 'success' criteria for all infants



Time (hours)	24	48	72	96	120	144	168	192	216	240
Number remaining (VCV)	33	24	21	15	13	10	8	7	6	6
Number remaining (VG)	25	19	15	12	11	9	9	9	7	7

Figure 4-4 Kaplan-Meier curves of time to 'success' criteria for all infants focusing on the first 240 hours

In the VG group the time taken to reach the 'success' criteria ranged from five hours to 1663 hours. In the VCV group the time taken to reach the 'success' criteria ranged from six hours to 1484 hours.

The median time to 'success' criteria in the VG group was 23 hours (95% CI 11 – 35 hours). In the VCV group, the median time to 'success' criteria was 36 hours (95% CI 18 – 54 hours). This result favours VG and represents a clinically relevant difference of 13 hours between groups in the time taken to be ready for extubation.

Although the median time to 'success' criteria favours VG the HR of 0.93 (95% CI 0.63 – 1.37) just favours VCV. The HR is close to one, indicating that there is little overall difference between the groups in the time to reach the 'success' criteria. A HR of 0.93 means that, at any time during the trial, infants in the VCV group had a seven per cent increased chance of reaching the 'success' criteria compared with infants in the VG group.

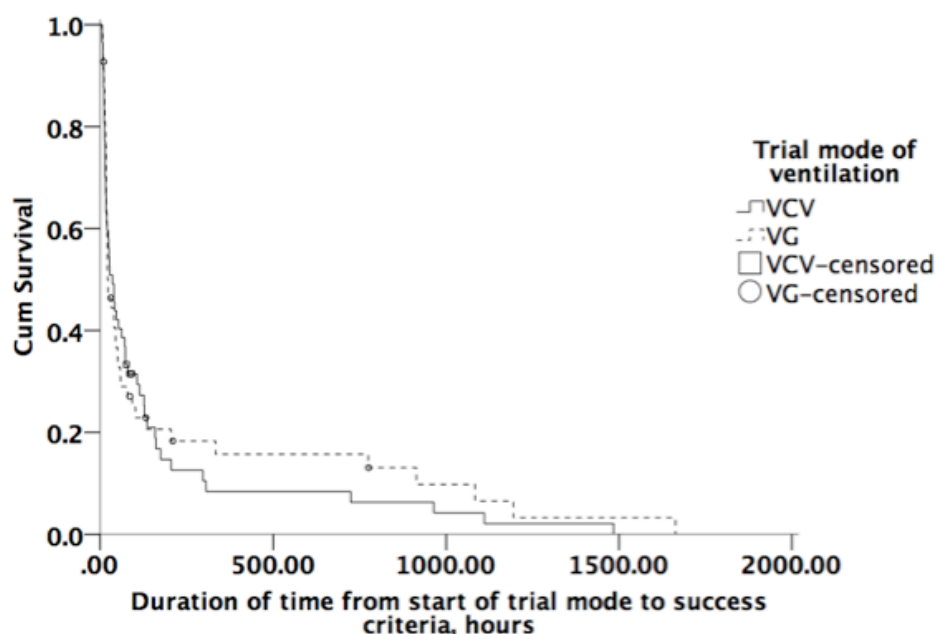
This discrepancy may be explained by examining the curves in greater detail and considering the rates at which infants reached the 'success' criteria earlier in the trial compared with later in the trial. Figure 4-4 shows that infants in the VG group reached the 'success' criteria at a faster rate than those in the VCV group between approximately 20 hours and 130 hours. This explains why the median time to 'success' criteria favours the VG group. After approximately 130 hours, infants in the VCV group reached the 'success' criteria at a faster rate than those in the VG group. In both groups very few infants had not yet reached the 'success' criteria by 160 hours. However, those infants account for the long 'tail ends' of the curves in Figure 4-3. It is those infants that likely influence the overall HR which presumes that the hazard rate remains constant at all time points (Parmar et al., 1995).

4.10.6 Effect of gestational age on the primary outcome

4.10.6.1 Infants born at <28 weeks' gestation

There were 54 infants in this sub-group. Twenty-seven were randomised to VCV and 27 to VG. In this sub-group, the time taken to reach the 'success' criteria ranged from six to 1484 hours (62 days) in the VCV group and five hours to 1663 hours (69 days) in the VG group.

Figure 4-5 shows the Kaplan-Meier curves of time to reach the 'success' criteria in infants born at <28 weeks' gestation. The median time to 'success' criteria was 79 hours (95% CI 0.0 – 177.71) in the VCV group and 102 hours (95% CI 0.0 – 204.69) in the VG group. This difference of 23 hours is clinically relevant. The HR was 0.76 (95% CI 0.42 – 1.37). This indicates that, at any time during the trial, infants in the VCV group had a 24% increased chance of reaching the 'success' criteria than infants in the VG group. The median time to 'success' criteria and the HR appear to favour VCV in this gestational age group. However, the 95% CIs reflect the large degree of uncertainty associated with these results in this sub-group.



Time (hours)	250	500	750	1000	1250	1500
Number remaining (VCV)	5	4	3	2	1	0
Number remaining (VG)	6	5	5	3	1	1

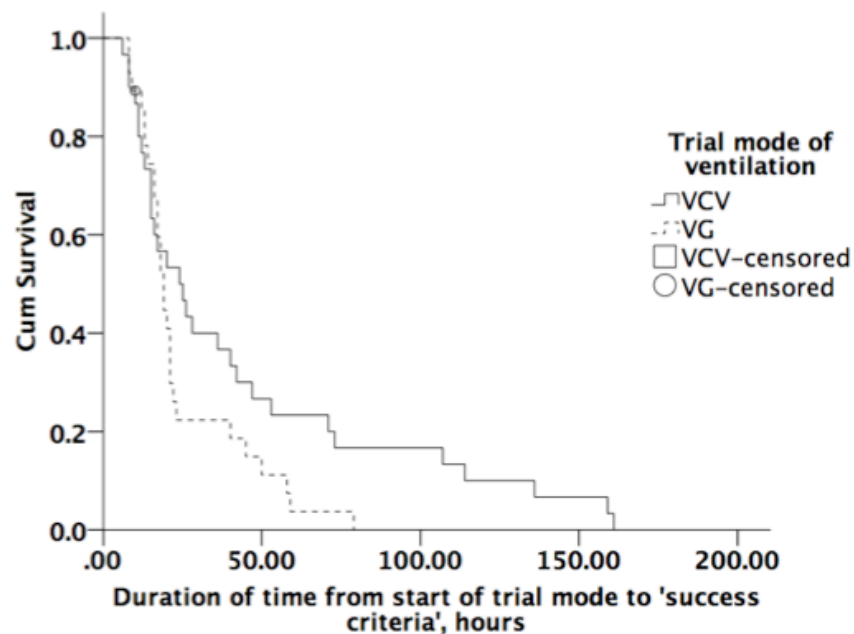
Figure 4-5 Kaplan-Meier curves of duration of time to 'success' criteria for infants born at <28 weeks' gestation

Infants born at <28 weeks' gestation accounted for all of the infants in the trial who had not yet reached the 'success' criteria after one week (168 hours). Seventeen infants had not reached the 'success' criteria by 168 hours. Five infants had not reached the 'success' criteria by 1000 hours.

Eight infants in this gestational age group had censored data. Three infants had been randomised to VCV; two died and one was transferred to another site before reaching the 'success' criteria. Five infants had been randomised to VG; two died and three were transferred to another site before reaching the 'success' criteria. Therefore the censoring of data due to death was balanced between groups. No deaths were attributed to the mode of ventilation (see Section 4.15 Serious Adverse Events).

4.10.6.2 Infants born at 28 – 33+6 weeks' gestation

There were 58 infants in this sub-group. Thirty infants were randomised to VCV and 28 to VG. Figure 4-6 shows the Kaplan-Meier curves for the time-to-event analyses of these infants. In this sub-group, the time taken to reach the 'success' criteria ranged from six to 161 hours in the VCV group and eight to 79 hours in the VG group.



Time (hours)	25	50	75	100	125	150	175
Number remaining (VCV)	14	8	5	5	3	2	0
Number remaining (VG)	6	3	1	0	0	0	0

Figure 4-6 Kaplan-Meier curves of time to 'success' criteria for infants born at 28 – 33+6 weeks' gestation

The median time to 'success' criteria was 24 hours (95% CI 11.9 – 36.1) in the VCV group and 19 hours (95% CI 16.5 – 21.5) in the VG group. The clinical relevance of a difference of five hours is unknown. However the HR was 1.6 (95% CI 0.92 – 2.82). This indicates that, at any time during the trial, infants in the VG group had a 60% increased chance of reaching the 'success' criteria than infants in the VCV group.

These results strongly favour VG in infants born within this gestational age group. They demonstrate a bigger treatment effect when modes are compared

than the effect seen in infants born at <28 weeks' gestation. In addition the 95% CIs are narrower and the lower CI is only just below one. These highlight the strength of the treatment effect of VG.

Only one infant in this gestational age group had censored data. That infant had been randomised to VG but the death was not attributed to the mode of ventilation.

4.10.7 Inborn infants

There were 88 inborn infants. Forty-three infants were randomised to VCV and 45 to VG. Figure 4-7 shows the Kaplan-Meier curves for the time-to-event analyses of these infants. In this sub-group, the time taken to reach the 'success' criteria ranged from six to 964 hours in the VCV group and eight to 1663 hours in the VG group.

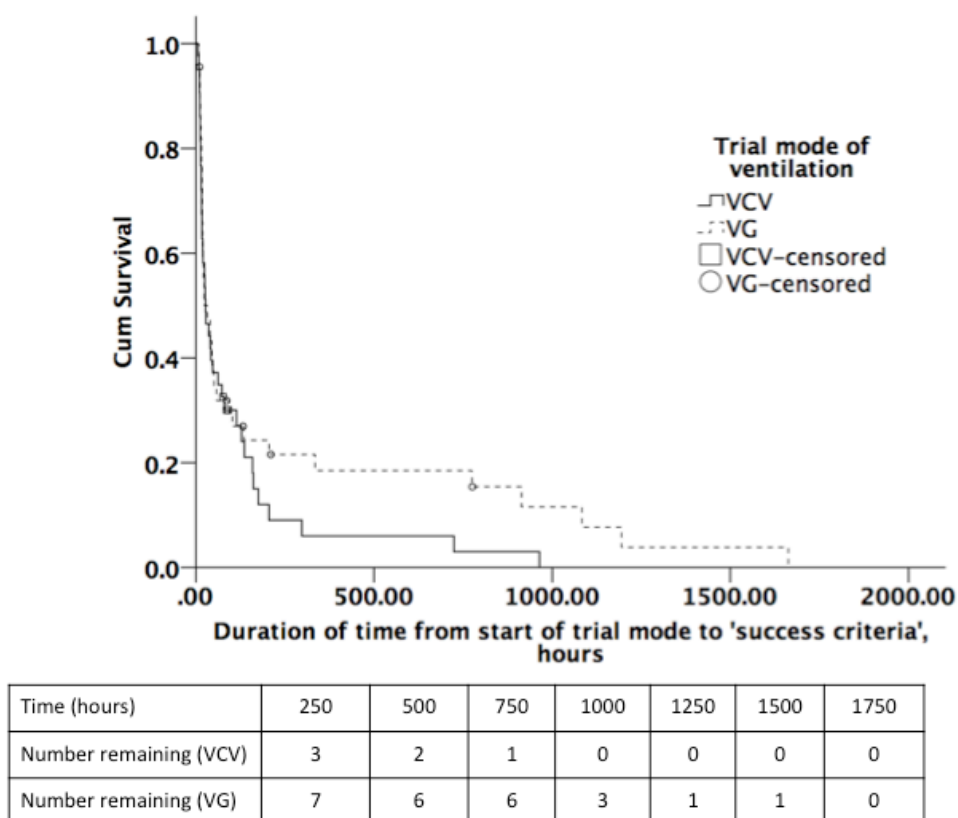


Figure 4-7 Kaplan-Meier curves of time to 'success' criteria for inborn infants

The median time to 'success' criteria was 25 hours (95% CI 12.6 – 37.4) in the VCV group and 32 hours (95% CI 13.5 – 50.5) in the VG group. The clinical relevance of a difference of seven hours is unknown. The HR was 0.76 (95% CI 0.48 – 1.2).

Therefore the median time to 'success' criteria and the HR appear to favour VCV in this gestational age group. However, the 95% CIs reflect the large degree of uncertainty associated with these results in this sub-group.

4.11 Effects of covariates on the primary outcome

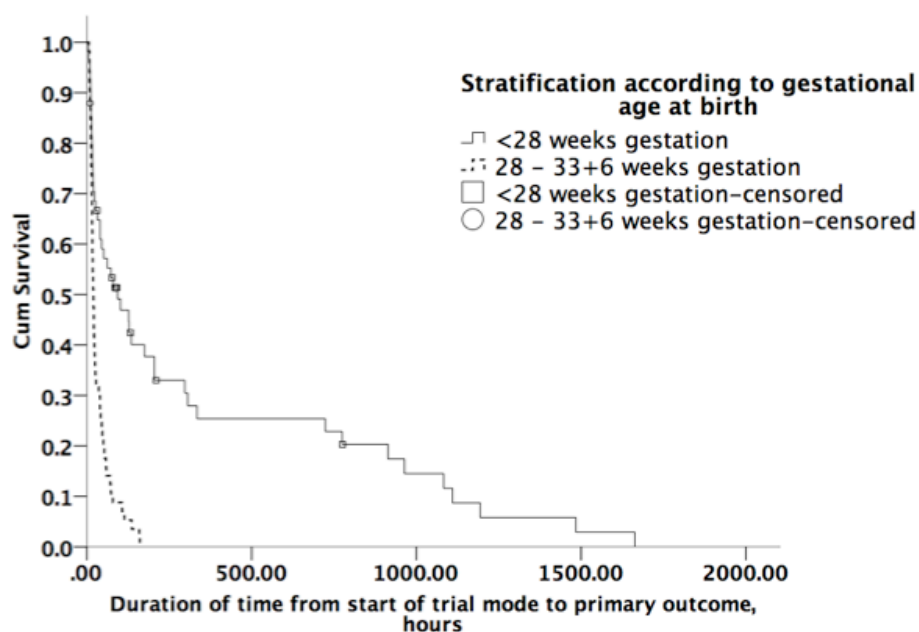
A Cox proportional hazards model was used to investigate the effects of covariates on the primary outcome. Univariable analyses were undertaken to analyse the effect of these variables on the time to reach the 'success' criteria. Multivariable analyses were then undertaken to investigate their effect on the HR of primary outcome. The covariates are listed here.

1. Gestational age (<28 weeks' gestation and 28-33+6 weeks' gestation)
2. The administration of two doses of maternal antenatal corticosteroids before delivery.
3. The administration of postnatal glucocorticosteroids (dexamethasone) to infants to facilitate extubation.
4. Surgical ligation of a PDA to facilitate extubation.

4.11.1 Gestational age as a covariate

Gestational age had been predicted to be a covariate that may influence the primary outcome. As such, it was used as a stratification factor prior to randomisation. Its effect on the primary outcome is presented here.

Figure 4-8 represents the Kaplan-Meier curves showing the effect of gestational age (either <28 weeks' gestation or 28 – 33+6 weeks' gestation) on the time to reach the 'success' criteria. The mode of ventilation has not been included in this curve. Therefore the dashed line represents the time to reach the 'success' criteria in all infants between 28 and 33+6 weeks' gestation, regardless of their mode of ventilation. The solid line shows the same for infants born at <28 weeks' gestation.



Time (hours)	250	500	750	1000	1250	1500	1750
Number remaining (<28 weeks' gestation)	13	10	9	5	2	1	0
Number remaining (28-33+6 week's gestation)	0	0	0	0	0	0	0

Figure 4-8 Kaplan-Meier curves showing the effect of gestational age on time to 'success' criteria

This figure demonstrates that infants born at 28 – 33+6 weeks' gestation reach the success criteria much quicker than infants born at <28 weeks' gestation. As has been discussed previously this was not unexpected. This figure justifies the decision to use gestational age as a stratification factor before randomisation.

Table 4-14 shows the results of univariable analysis investigating the effect of gestational age on the time to reach 'success' criteria. It demonstrates that gestational age had a strong effect on the primary outcome. There was a very large difference in the median time to reach the 'success' criteria. At any time during the trial, infants in the 28 - 33+6 weeks' gestational age group had a three fold increase in the chance of reaching the 'success' criteria than those in the <28 weeks' gestation group. The 95% CIs of the HR do not cross below 1. Therefore these results strongly favour the effect of the 28 – 33+6 weeks' gestation variable on the primary outcome.

Factor	Level	Median time to 'success' criteria, hours (95% CI)	HR (95% CI)
Gestational age	< 28 weeks (reference variable)	93 (9.75 – 176.25)	1.00
	28 – 33+6 weeks (comparator variable)	20 (16.72 – 23.28)	3.32 (2.1 – 5.25)

Table 4-14 Univariable analysis of the effect of gestational age on the time to reach the 'success' criteria using the Cox proportional hazards model

CI, confidence interval; HR, hazard ratio

The multivariable analysis is shown in Table 4-15. This table demonstrates that the chance of reaching the 'success' criteria (the hazard) according to the mode of ventilation was altered when gestational age was taken into account.

Factor	Level	Adjusted HR (95% CI)
Arm	VCV (reference variable)	1.00
	VG (comparator variable)	1.066 (0.72 – 1.59)
Gestational age	< 28 weeks (reference variable)	1.00
	28 – 33+6 weeks (comparator variable)	3.36 (2.11 – 5.34)

Table 4-15 Multivariable analysis of the effect of gestational age on the time to reach the 'success' criteria using the Cox proportional hazards model

HR, hazard ratio; CI, confidence interval

As discussed previously, when analysing the effect of trial mode alone, the HR for the whole population was 0.93. When adjusted for gestational age, the HR became 1.066. This indicates that infants had a 6% greater chance of reaching the 'success' criteria in the VG arm when the effects of gestational age were taken into account. The HR changed from one that originally appeared to favour VCV to one that favoured VG when adjusted for gestational age.

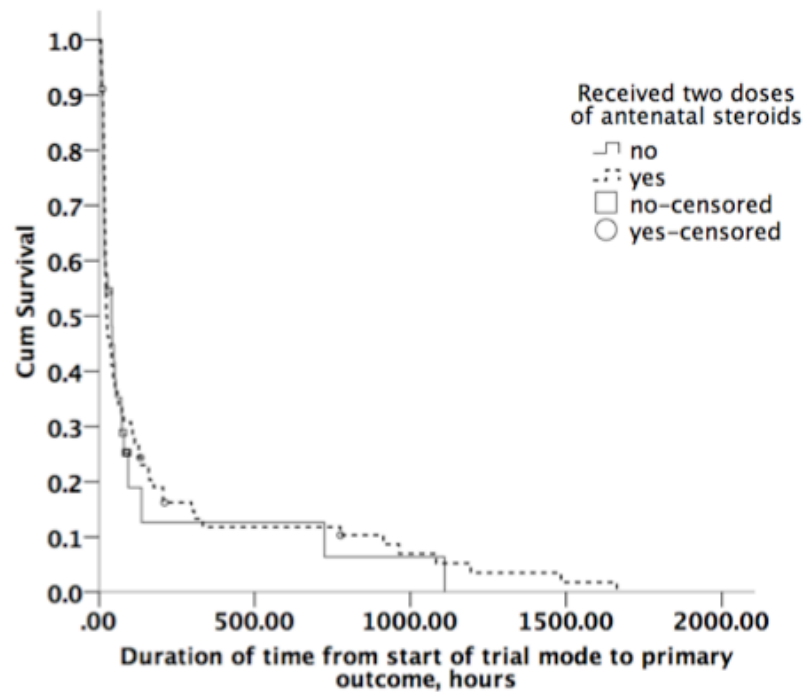
These results demonstrate that, when accounting for gestational age, infants reached the 'success' criteria faster in the VG group. Gestational age has a strong effect on the time taken to be ready for extubation. Therefore these results strongly support further investigation of the effect of gestational age when designing a larger trial.

4.11.2 Exposure to antenatal corticosteroids as a covariate

Administration of antenatal corticosteroids to women in preterm labour improves certain important outcomes in preterm infants, including a reduction in the incidence of RDS and in the need for mechanical ventilation (Roberts et al., 2017). Therefore it was predicted to be a covariate that might reduce the time to reach 'success' criteria in infants who had been exposed to antenatal corticosteroids.

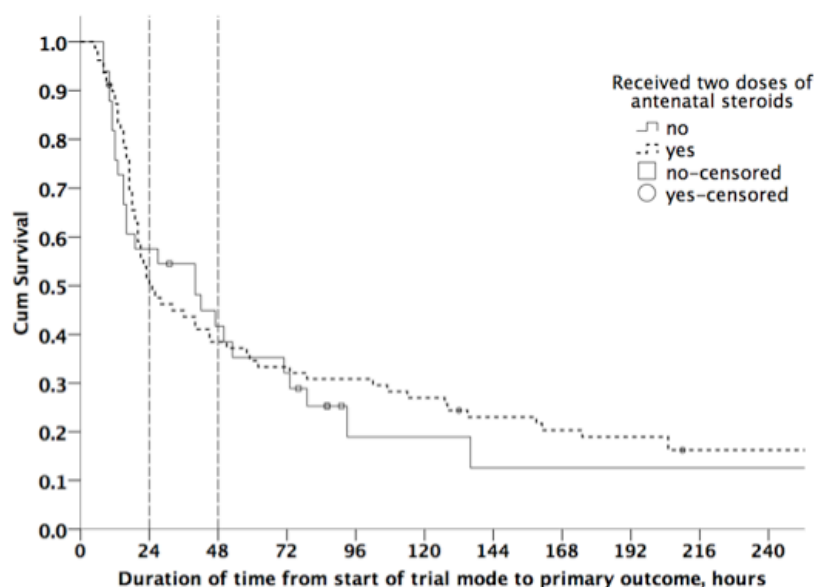
A complete course of antenatal corticosteroids at the trial site consisted of two doses of betamethasone, with the second dose being given at least 24 hours and up to seven days before delivery of the infant. The medical records of both inborn and outborn infants in this trial commonly recorded the numbers of doses administered to mothers and the dates at which they were administered but not the timings. Therefore for the purpose of this trial, a complete course was considered to be two doses of maternal corticosteroids administered up to one week before the birth of the infant.

Figure 4-9 and Figure 4-10 show the Kaplan-Meier curves for the time-to-event analyses according to exposure to maternal antenatal corticosteroids. Both curves represent the same data and analysis. Figure 4-9 shows the entire curves. Figure 4-10 focuses on the first 240 hours.



Time (hours)	250	500	750	1000	1250	1500	1750
Number remaining (received two doses of antenatal steroids)	11	8	8	4	2	1	0
Number remaining (did not receive two doses of antenatal steroids)	2	2	2	1	0	0	0

Figure 4-9 Kaplan-Meier curves showing the effect of two doses of antenatal corticosteroids on time to 'success' criteria



Time (hours)	24	48	72	96	120	144	168	192	216	240
Number remaining (received two doses of antenatal steroids)	39	30	26	24	21	17	15	14	11	11
Number remaining (did not receive two doses of antenatal steroids)	19	13	10	3	3	2	2	2	2	2

Figure 4-10 Kaplan-Meier curves showing the effect of two doses of antenatal corticosteroids on time to 'success' criteria focusing on the first 240 hours

Seventy-nine infants were exposed to two doses of maternal antenatal corticosteroids. Thirty-three infants were not exposed to two doses. These Kaplan-Meier curves show that the administration of two doses of antenatal corticosteroids did not appear to effect the time to reach the 'success' criteria. However, Figure 4-10 shows that the Kaplan Meier curves cross each other several times, violating the assumption that the hazard risk remains constant over time.

Table 4-16 shows that the median time to 'success' criteria when infants were exposed to two doses of antenatal corticosteroids was 25 hours. In infants not exposed to two doses, it was 40 hours. However, the HR favours the group who were not exposed to antenatal corticosteroids. This discrepancy may be related to the small number of infants in each sub-group. The wide CIs highlight the lack of certainty about these results.

Factor	Level	Median time to 'success' criteria, hours (95% CI)	HR (95% CI)
Two doses of maternal antenatal corticosteroids	No (reference variable)	40 (8.81 – 71.19)	1.00
	Yes (comparator variable)	25 (13.12 – 36.88)	0.89 (0.57 – 1.38)

Table 4-16 Univariable analysis of the effect of administration of maternal antenatal corticosteroids on the time to reach the 'success' criteria using the Cox proportional hazards model

CI, confidence interval; HR, hazard ratio

The multivariable analysis is shown in Table 4-17. This table demonstrates that the original HR comparing the trial modes was not altered when adjusted for exposure to two doses of antenatal corticosteroids. Therefore, a complete course of antenatal corticosteroids did not improve the chance of reaching the 'success' criteria. This was unexpected, however there is a high degree of uncertainty related to these results as highlighted by the wide CIs that cross 1. It is also important to consider that antenatal corticosteroids are associated with improved lung function in the first week of life but not after that (McEvoy et al., 2008). As some infants in this trial remained ventilated for many weeks, this is a possible reason for the apparent lack of benefit to infants in this trial

Factor	Level	Adjusted HR (95% CI)
Arm	VCV (reference variable)	1.00
	VG (comparator variable)	0.95 (0.63 – 1.43)
Two doses of antenatal steroids	No (reference variable)	1.00
	Yes (comparator variable)	0.9 (0.57 – 1.43)

Table 4-17 Multivariable analysis of the effect of two doses of maternal antenatal corticosteroids on the time to reach the 'success' criteria using the Cox proportional hazards model

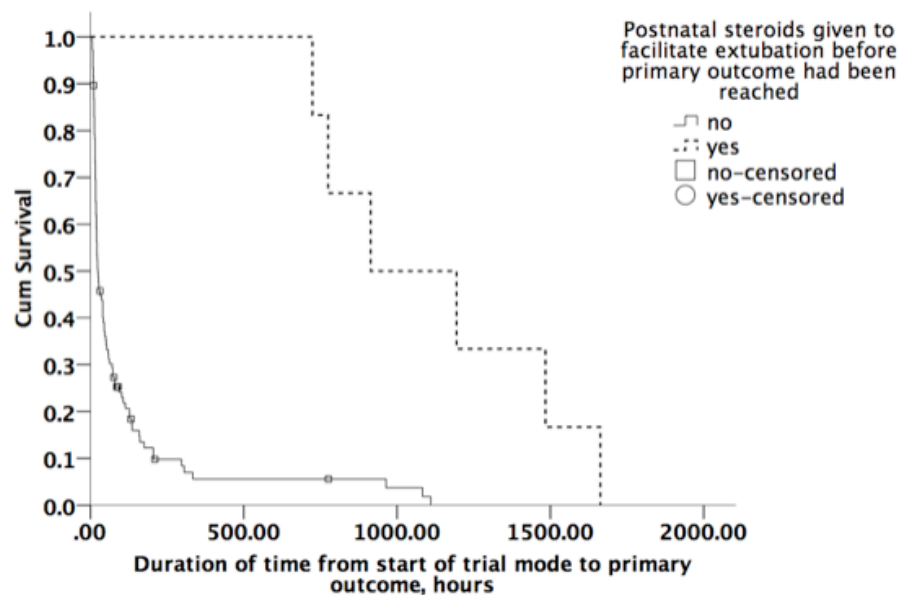
HR, hazard ratio; CI, confidence interval

4.11.3 Use of postnatal corticosteroids as a covariate

Postnatal corticosteroids have benefits in weaning ventilation and facilitating extubation in ventilated infants (Doyle et al., 2017b). At the trial site they are used for infants who have severe lung disease associated with prematurity and have been ventilated for prolonged periods. At the trial site corticosteroids are not given for this purpose until infants have remained ventilated for over a week, and often longer than that (Doyle et al., 2017b).

One potential effect in using them in this way is that they enable a ventilator-dependent infant to be ready for extubation more quickly than might otherwise be the case. Therefore their use was considered to be a covariate that could potentially influence the primary outcome.

Figure 4-11 shows the Kaplan-Meier curves showing the effect of postnatal corticosteroids on the time to reach the 'success' criteria. Only six infants received postnatal corticosteroids during the trial compared with 106 infants who did not.



Time (hours)	250	500	750	1000	1250	1500	1750
Number remaining (postnatal steroids given)	5	5	4	3	2	1	0
Number remaining (postnatal steroids not given)	7	4	4	2	0	0	0

Figure 4-11 Kaplan-Meier curves showing the effect of postnatal corticosteroids on time to 'success' criteria

This figure appears to show that the use of postnatal corticosteroids does not favour the primary outcome. This is matched by the median times to 'success' criteria and HR shown in Table 4-18 that do not favour the use of postnatal corticosteroids on the primary outcome. However, very few infants received corticosteroids and the CIs are very wide, meaning that there is a high degree of uncertainty about these results.

The results reflect the fact that postnatal corticosteroids were given to the infants who were ventilator-dependent for prolonged periods. The primary outcome for these infants ranged from 724 hours to 1662 hours. Therefore, these results demonstrate the effect of the severity of lung disease on the primary outcome rather than the effect of the postnatal corticosteroids on the primary outcome. As a result of this, and due to the very small numbers of infants exposed to this variable, a multivariable analysis was not undertaken.

Factor	Level	Median time to 'success' criteria, hours (95% CI)	HR (95% CI)
Received postnatal steroids	No (<i>reference variable</i>)	24 (13.99 – 34.01)	1.00
	Yes (<i>comparator variable</i>)	914 (411.1 – 1416.91)	0.127 (0.04 – 0.42)

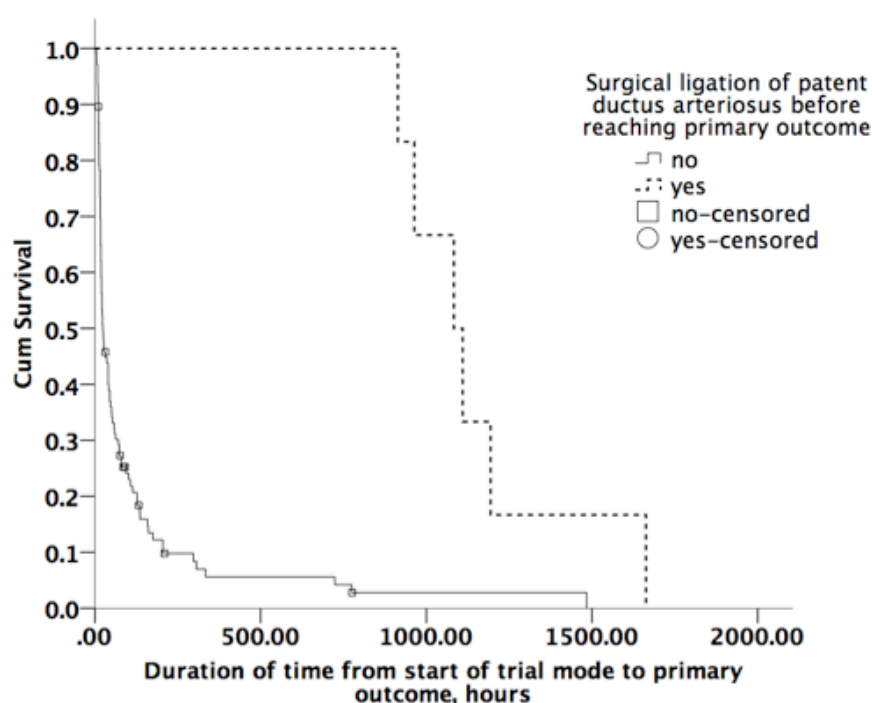
Table 4-18 Univariable analysis of the effect of postnatal corticosteroids on the time to reach the 'success' criteria using the Cox proportional hazards model

CI, confidence interval; HR, hazard ratio

4.11.4 Effect of surgical PDA ligation as a covariate

A persistent PDA can prolong the need for mechanical ventilation (Clyman , 2013). Six infants in the trial underwent cardiothoracic surgery to ligate their persistent PDAs. This surgery was considered necessary because the persistent PDAs were considered to be contributing to these infants' need for prolonged ventilation. Therefore this was considered to be a covariate that may influence the primary outcome.

Figure 4-12 shows the Kaplan-Meier curves showing the effect of PDA ligation on the time to reach the 'success' criteria. It appears to show that PDA ligation does not favour the primary outcome. This is matched by the median times to 'success' criteria and HR shown in Table 4-19 that do not favour the effect of PDA ligation on the primary outcome.



Time (hours)	250	500	750	1000	1250	1500	1750
Number remaining (had surgical ligation of PDA)	5	5	5	3	1	1	0
Number remaining (did not have surgical ligation of PDA)	7	4	3	1	1	0	0

Figure 4-12 Kaplan-Meier curves showing the effect of PDA ligation on time to 'success' criteria

However, the results again reflect the fact that PDA ligation was only used for infants who were ventilator-dependent for prolonged periods. The primary outcome for these infants ranged from 914 to 1662 hours. The results demonstrate the effect of the severity of lung disease on the primary outcome rather than PDA ligation as an influential covariate. As a result of this, and due to the very small numbers of infants exposed to this variable, a multivariable analysis was not undertaken.

Factor	Level	Median time to 'success' criteria, hours (95% CI)	HR (95% CI)
Received surgical PDA ligation	No <i>(reference variable)</i>	24 (13.99 – 34.01)	1.00
	Yes <i>(comparator variable)</i>	1083 (907.76 – 1258.24)	0.162 (0.061 – 0.432)

Table 4-19 Univariable analysis of the effect of postnatal corticosteroids on the time to reach the 'success' criteria using the Cox proportional hazards model

PDA, patent ductus arteriosus; CI, confidence interval; HR, hazard ratio

4.12 Secondary outcome measures

The results of analyses of secondary outcome measures are presented here. For all analyses involving HRs and ORs, VCV is the reference variable and VG is the comparator variable.

4.12.1 Respiratory outcome measures

	VG n = 55	VCV n = 57	HR / OR* (95% CI)
Total duration of ventilation before first extubation, hours, median (95% CI)	32 (12.53 – 51.47)	41 (15.68 – 66.32)	HR 0.85 (0.56 – 1.27)
Reintubated within 72 hours of first extubation, n (%)			
yes	10 (18.2)	7 (12.3)	OR 1.65 (0.57 – 4.77)
no	38 (69.1)	44 (77.2)	
data censored during first period of ventilation	7 (12.7)	6 (10.5)	
Total duration of mechanical ventilation before discharge, hours, median (95% CI)	50 (16.27 – 83.72)	98 (31.8 – 164.21)	HR 0.86 (0.57 – 1.29)
Pulmonary air leak (pneumothorax or PIE) occurring whilst on trial mode of ventilation, n (%)	5 (9)	10 (18)	OR 0.47 (0.15 – 1.48)
Pneumothorax occurring whilst on trial mode, n (%)	1 (2)	7 (12)	OR 0.13 (0.02 – 1.11)
PIE occurring whilst on trial mode, n (%)	5 (9)	4 (7)	OR 1.33 (0.34 – 5.22)
Number of episodes of hypocarbia (pCO ₂ <4.0kPa) at any time			
median (IQR)	0 (0 – 2)**	0 (0 – 2)	OR 0.88 (0.62 – 1.28)
0 episodes (%)	25 (46.2)**	30 (52.6)	
≥1 episode (%)	29 (53.7)**	27 (47.4)	
Number of episodes of hypocarbia whilst on the trial mode			
median (IQR)	0 (0 – 2)**	0 (0 – 2)	OR 0.84 (0.56 – 1.26)
0 episodes (%)	27 (50)**	33 (57.9)	
≥1 episode (%)	27 (50)**	24 (42.1)	

Number of infants requiring HFOV, n (%)	7 (13)	6 (11)	OR 1.24 (0.39 – 3.95)
Duration of NIV in infants who received it, days, median (IQR)	12 (4.2 – 19.8) (49 survivors)	19 (11.7 – 26.3) (51 survivors)	HR 0.95 (0.63 – 1.43)
Need for respiratory support or supplemental at 28 days of life (survivors only), n (%)	35 (70) (50 survivors)	36 (67.9) (53 survivors)	OR 1.1 (0.48 – 2.54)
Need for respiratory support or supplemental oxygen at 36 weeks' CGA (survivors only), n (%)	30 (60) (50 survivors)	28 (52.8) (53 survivors)	OR 1.34 (0.61 – 2.93)
Chronic lung disease requiring home oxygen therapy (survivors only), n (%)	20 (40.8) (49 survivors)	20 (37.7) (53 survivors)	OR 1.14 (0.51 – 2.52)
Need for positive pressure respiratory support at home, n (%)	0	0	N/A

Table 4-20 Comparison of data on respiratory outcomes

HR, hazard ratio; OR, odds ratio; CI, confidence interval; n, number; NICU, neonatal intensive care unit; PIE, pulmonary interstitial emphysema; IQR, interquartile range; N/A, not applicable; kPA, kilopascals; NIV, non-invasive ventilation; HFOV, high frequency oscillatory ventilation; CGA, corrected gestational age;

*Hazard ratios are used for time-to-event data. Odds ratios are used for binary data. ** Data missing for one patient

4.12.2 Duration of ventilation

There were no obvious differences between groups in the total duration of ventilation until first extubation, and the total duration of ventilation before discharge. The HRs favoured VCV but the median values favoured VG.

However the CIs for these outcome measures are wide and cross 1, highlighting the lack of certainty regarding these results. During any period of ventilation the data from 15 infants were censored due to death or transfer to another hospital whilst ventilated. Eleven of these infants were in the VCV group and four were in the VG group. Similar numbers of infants required HFOV at any time during the trial.

4.12.3 Pulmonary air leak

There were no statistically significant differences between groups in the pulmonary air leak data. However, absolute differences were apparent. Twice as many infants in the VCV group (18%) developed either PIE or a pneumothorax whilst on the trial mode compared with those in the VG group (9%). When analysed further, the difference can be attributed to the data on pneumothoraces. Eight infants developed a pneumothorax whilst on the trial mode and, of these, seven were in the VCV group and one was in the VG group. The wide CIs are probably due to the small numbers of these outcomes.

Of the seven infants in the VCV group who developed a pneumothorax, four were born at <28 weeks' gestation and three were born at ≥28 weeks' gestation. The infant in the VG group who developed a pneumothorax was born at <28 weeks' gestation. All infants who developed PIE were born at <28 weeks' gestation.

These numbers are small but this is an important finding in a trial of VTV modes. The aim of using VTV is to avoid volutrauma which contributes to VALI. A pneumothorax has been referred to as macroscopic evidence of barotrauma. However, excessive expansion of the lungs due to excessive tidal volumes may also cause pneumothoraces. Therefore this is an important outcome measure to explore further in a larger trial.

4.12.4 Hypocarbia

Hypocarbia, defined in this trial as a pCO₂ of <4kPa measured on blood gas analysis, can be a side effect of ventilation. It can represent excessive expansion of the lungs due to excessive tidal volumes. In preterm infants, hypocarbia has been associated with brain injury (Okumura et al., 2001; Erickson et al., 2002). This is a serious side effect in infants whose brains are already at risk of injury due to antenatal, perinatal and postnatal events.

Therefore it is important to avoid hypocarbia when ventilating preterm infants.

In this trial there were no differences between groups in the numbers of documented episodes of hypocarbia. Fifty-four per cent of infants in the trial did not have any documented episodes of hypocarbia. The protocol did not mandate the timings of blood gas analyses and the treating clinical teams

decided on their timings as part of individualised patient care. Therefore the number and frequency of blood gas analyses varied with each patient.

VTV has been shown to reduce the frequency of hypocarbia when compared with PLV (Keszler et al., 2004; Cheema et al., 2007). It is reassuring that no differences were seen between two modes of VTV in this trial. However as hypocarbia can reflect excessive tidal volume delivery it would need to be investigated further as a secondary outcome measure in a larger trial.

4.13 Secondary outcomes: mortality and neurological outcomes

The numbers of infants who died or developed severe IVH or PVL were small and were similar between groups. The overall mortality rate was similar to that of the trial site (Garg, 2014).

	VCV n = 57	VG n = 55	OR (95% CI)
Death before discharge from hospital, n (%)	4 (7)	6 (10.9)	1.62 (0.43 – 6.09)
Severe IVH (Papile grades 3-4), n (%)	7 (12.3)	3 (5.5)*	0.42 (0.1 – 1.71)
PVL, n (%)	3 (5.3)	4 (7.3)*	1.44 (0.31 – 6.76)

Table 4-21 Comparison of data on mortality and neurological outcomes

n, number; OR, odds ratio; IVH, intraventricular haemorrhage; PVL periventricular leukomalacia

* Data missing for one infant

4.14 Secondary outcomes: other important outcomes of prematurity

There were similar numbers of infants developing other important outcomes of prematurity. There were three additional infants requiring PDA ligation in the VG group. The proportion of infants requiring laser therapy for ROP is similar to that reported from the trial site in 2014 (Garg, 2014).

	VCV n = 57	VG n = 55	OR (95% CI)
ROP requiring laser therapy (survivors only), n (%)	6 (11.3)* (53 survivors)	10 (20) § (50 survivors)	2.02 (0.67 – 6.06)
PDA requiring medical or surgical treatment, n (%)	14 (24.6)	15 (27.3) §	1.21 (0.52 – 2.83)
PDA requiring surgical treatment, n (%)	3 (5.3)	6 (10.9) §	2.3 (0.54 – 9.7)
NEC (modified Bell's stage 2 or greater), n (%)	4 (7)	4 (7.3)	1.04 (0.25 – 4.38)
Intestinal perforation without NEC, n (%)	1 (1.8)	0 (0)	0.0
Confirmed infection, n (%)	15 (26.3)	16 (29.1)	1.15 (0.5 – 2.63)

Table 4-22 Comparison of data on other outcomes of prematurity

N, number; OR, odds ratio; ROP, retinopathy of prematurity; PDA, patent ductus arteriosus; NEC, necrotising enterocolitis.

* Data missing for one infant; § Data missing for two infants

4.15 Serious adverse events

The expected serious adverse events (SAEs) are outlined in Table 4-23. There were no suspected unexpected serious adverse events (SUSARs).

The rates of chronic lung disease are calculated according to the numbers of infants who survived to 36 weeks' gestational age. In the VG group, six infants died but one of those survived beyond 36 weeks' corrected gestational age. Therefore the denominator number in that group is 50. In the VCV group, four infants died, all of whom died within the first two weeks of life. Therefore, the denominator number in that group is 53.

The rates of retinopathy of prematurity (ROP) were calculated according to the numbers of infants who survived to receive ROP screening. This was the same as the numbers of infants who survived until 36 weeks' corrected gestational age. Therefore the denominator numbers are 50 for the VG group and 53 for the VCV group.

Serious expected adverse events	VG n = 55	VCV n = 57	Total population n = 112
Death before discharge from hospital, n (%)			
Yes	6 (10.9)	4 (7)	10 (8.9)
No	49 (89.1)	53 (93)	102 (91.1)
Chronic lung disease (survivors only), n (%)			
Yes	30 (60)	28 (52.8)	58 (56.3)
No	20 (40) (50 survivors)	25 (47.2) (53 survivors)	45 (43.7) (103 survivors)
Reintubation after initial extubation, n (%)			
Yes	10 (18.2)	7 (12.3)	17 (15.2)
No	38 (69.1)	44 (77.2)	82 (73.2)
Data censored during first period of ventilation	7 (12.7)	6 (10.5)	13 (11.6)
Pulmonary air leak after enrolment into trial, n (%)			
Yes	2 (3.6)	9 (15.8)	11 (9.8)
No	53 (96.4)	48 (84.2)	101 (90.2)
Episodes of hypocarbia (pCO ₂ <4.0kPa) per infant on any mode of ventilation after randomisation into trial, n (%)			
No episodes	25 (45.5)	30 (52.6)	55 (49.1)
One episodes	12 (22.2)	6 (10.5)	18 (16.1)
Two episodes	7 (12.7)	7 (12.3)	14 (12.5)
Three episodes	4 (7.4)	2 (3.5)	6 (5.4)
Four episodes	2 (3.7)	5 (8.8)	7 (6.2)
Five episodes	2 (3.7)	2 (3.5)	4 (3.6)
Six episodes	1 (1.9)	2 (3.5)	3 (2.7)
Seven episodes	0 (0)	2 (3.5)	2 (1.8)
Eight episodes	1 (1.9)	0 (0)	1 (0.9)
Fourteen episodes	0 (0)	1 (1.8)	1 (0.9)
Missing data	1 (1.9)	0 (0)	1 (0.9)
Episodes of hypocarbia (pCO ₂ <4.0kPa) per infant on trial mode of ventilation only after randomisation into trial, n, (%)			
No episodes	27 (49.1)	33 (57.9)	60 (53.6)
One episode	12 (21.8)	6 (10.5)	18 (16.1)
Two episodes	7 (12.7)	6 (10.5)	13 (11.6)
Three episodes	3 (5.5)	3 (5.3)	6 (5.4)
Four episodes	3 (5.5)	5 (8.8)	8 (7.1)
Five episodes	1 (1.8)	0 (0)	1 (0.9)
Six episodes	0 (0)	1 (1.8)	1 (0.9)

Seven episodes	0 (0)	3 (5.3)	3 (2.7)
Eight episodes	1 (1.8)	0 (0)	1 (0.9)
Missing data	1 (1.8)	0 (0)	1 (0.9)
Episodes of pulmonary haemorrhage after randomisation, n, (%)			
No episodes	50 (91)	52 (91.2)	102 (9.1)
One episode	3 (5.4)	4 (7)	7 (6.3)
Two episodes	2 (3.6)	1 (1.8)	3 (2.6)
NEC, (≥ Bell's Stage 2) n, (%)			
Yes	4 (7.3)	4 (7)	8 (7.1)
No	51 (92.7)	53 (93)	104 (92.9)
Intestinal perforation without NEC, n (%)			
Yes	0 (0)	2 (3.5)	2 (1.8)
No	0 (0)	55 (96.5)	110 (98.2)
Intracranial haemorrhage or white matter damage seen on cranial ultrasound scan, n (%)			
Yes	6 (10.9)	9 (15.8)	15 (13.4)
No	48 (87.3)	48 (84.2)	96 (85.7)
Missing data	1 (1.8)	0 (0)	1 (0.9)
PDA treated medically, n (%)			
Yes	9 (16.4)	11 (19.3)	20 (17.9)
No	45 (81.8)	46 (80.7)	91 (81.3)
Missing data	1 (1.8)	0 (0)	1 (0.9)
PDA treated surgically, n (%)			
Yes	6 (10.9)	3 (5.3)	9 (8)
No	47 (85.5)	54 (94.7)	101 (90.2)
Missing data	2 (3.6)	0 (0)	2 (1.8)
Any ROP, (survivors only), n (%)			
Yes	20 (40)	24 (45.3)	44 (42.7)
No	27 (54)	28 (52.8)	55 (53.4)
Missing data	3 (6) (50 survivors)	1 (1.9) (53 survivors)	4 (3.9) (103 survivors)
ROP requiring treatment (survivors only), n (%)			
Yes	10 (20)	6 (11.3)	16 (15.5)
No	37 (74)	46 (86.8)	83 (80.6)
Missing data	3 (6) (50 survivors)	1 (1.9) (53 survivors)	4 (3.9) (103 survivors)

Table 4-23 Expected serious adverse events (SAEs)

4.16 Comparison of SAE rates in the trial with the population at the trial site

There were no major differences between groups in rates of SAEs. In the VG group, 42 infants (76.4%) had at least one SAE although in another three infants data on one SAE were missing. Forty-five infants (78.9%) in the VCV group had at least one SAE. There were no safety concerns raised in relation to the interventions or trial protocol.

The trial site produces an annual report on important clinical outcomes of infants admitted to the site. The annual report published in 2014 stated that, from 2012 – 2014, 90% of infants born at ≤ 31 weeks' gestation survived to discharge home (Garg, 2014). In this trial, 91.1% of infants survived to discharge home. Therefore the mortality rate for infants in this trial was no different to that reported by the unit.

In 2014, 14.2% of infants born ≤ 30 weeks' gestation and admitted to the trial site received laser therapy for ROP (Garg, 2014). The rate in this trial over a period of 29 months was similar (15.5%). The annual report also states that 14% of infants born at < 30 weeks' gestation underwent PDA ligation in 2014, compared with only 8% of infants in this trial. In 2014, 9% of infants at the trial site developed NEC, similar to the proportion of 7.1% in this trial.

The annual report also states that 30% of infants born at < 32 weeks' gestation were diagnosed with chronic lung disease (oxygen requirement at 36 weeks' corrected gestational age). In this trial, 56.3% of infants had this diagnosis. This difference may be explained by the fact that this trial included infants born between 32 and 33+6 weeks' gestation. Many infants in this trial were transferred to other hospitals for ongoing care after their initial period of intensive care. Data on these infants were requested from these other sites as stated in the trial protocol. Other units have differing practices regarding respiratory care which may have contributed to the higher rates of chronic lung disease. As this is such an important diagnosis in preterm infants, further investigation of this outcome would be essential in a larger trial.

These data demonstrate that the rates of SAEs were balanced between groups and were mostly similar to overall rates reported at the trial site.

4.17 Duration of ventilation for non-enrolled infants

During the trial period from July 2013 to December 2015, 47 infants were born at <34 weeks' gestation, were ventilated for RDS, and remained at the trial site for ongoing intensive care. These infants were not enrolled into the trial. They included the 46 infants for whom consent was not obtained and one infant who had been enrolled but was subsequently withdrawn due to the postnatal diagnosis of an underlying congenital condition.

The trial unit, The James Cook University Hospital Neonatal Unit, uses an electronic platform, BadgerNet Neonatal (Clevermed Ltd), to routinely record clinical data on all infants both prospectively and retrospectively. This is done as part of the UK Neonatal Collaborative. Data on all infants admitted to the unit are recorded in this platform as part of standard neonatal care.

Data on infants not enrolled into the trial were not collected by the research team for the purposes of the trial. However, data on the duration of the first period of ventilation for non-enrolled infants ventilated during the trial period were obtained from the BadgerNet Neonatal platform. These data were used to provide a degree of comparison with enrolled infants in order to ascertain whether the enrolled infants were representative of the unit population as a whole.

It was not possible to obtain information on the type of ventilation that each of the non-enrolled infants received but most would have received either VCV or VG. This is because the standard mode of ventilation in the neonatal unit at the time was VCV, and because, after the change in the consent process, infants were randomised to either VCV or VG before deferred consent was sought.

There were some important differences between the data on enrolled infants collected specifically for the trial and the routinely recorded data on non-enrolled infants held in the BadgerNet Neonatal platform. These are listed below.

- The primary outcome on enrolled infants was the time taken to reach the 'success' criteria. This was used as an objective measure to represent 'readiness for extubation' rather than the subjective measure of duration of ventilation until extubation. Data on non-enrolled infants were only available as duration of initial period of ventilation until extubation.

Therefore, to compare the two groups, duration of ventilation was used rather than time to 'success' criteria.

- The data on duration of ventilation for enrolled infants were recorded in hours whereas data on duration of ventilation for non-enrolled infants were only available in days. Therefore, to compare the two groups, the duration of ventilation for enrolled infants was converted from hours to days. Enrolled infants who were ventilated for ≤ 24 hours had their duration of ventilation converted to one day; enrolled infants who were ventilated for ≤ 48 hours had their duration of ventilation converted to two days, and so on.
- The primary outcome data on enrolled infants were analysed as survival data because censored data were known and documented accordingly. This was not possible using routinely held data from the BadgerNet Neonatal platform as information on censoring was not available. Therefore data on duration of ventilation for non-enrolled infants could only be analysed using descriptive analyses (such as medians) rather than survival analysis.

Therefore, the data on non-enrolled infants were not directly comparable to those on enrolled infants. However, they did provide some approximation on whether the enrolled infants were representative of the unit population.

Comparisons of the data are shown in Table 4-24.

Group/Sub-group	Duration of initial episode of ventilation in enrolled infants, days, median (IQR)	Duration of initial episode of ventilation in non-enrolled infants, days, median (IQR)
All infants	2 (1 – 5.8)	3 (2 – 11)
Infants born at <28 weeks' gestation	4 (1 – 19)	8 (3 – 34.8)
Infants born at 28 – 33+6 weeks' gestation	1 (1 – 2.3)	2 (2 – 3)

Table 4-24 Comparison of duration of initial episode of ventilation in enrolled and non-enrolled infants

These comparisons show that there was a trend towards shorter periods of ventilation in enrolled infants compared with non-enrolled infants. These are exploratory data. When designing a larger trial, it would be useful to consider how to collect data on non-enrolled infants in order to ascertain whether the trial population are truly representative of the denominator population.

4.18 Summary

There was a clinically relevant difference between groups in the median time taken to be ready for extubation. The median time taken to reach the 'success' criteria was 13 hours sooner in the VG group compared to the VCV group. The majority of infants reached the 'success' criteria within the first 48 hours. There was a difference between the groups in infants born at 28-33+6 weeks' gestation, with those in the VG group reaching the 'success' criteria faster. Gestational age had a marked effect on the time to be ready for extubation, with those born at 28-33+6 weeks' gestation reaching the 'success' criteria much faster than those born at <28 weeks' gestation. This validates the use of gestational age as a stratification factor.

Chapter 5 Ancillary Study

5.1 Introduction

This ancillary study was undertaken as part of a process evaluation of The VoluVent Trial to test the validity of the primary outcome (Oakley et al., 2006). This is good practice in trials of complex interventions (Craig et al., 2008; Moore et al., 2015)

The primary outcome measure of The VoluVent Trial was the duration of time taken from starting the trial mode until reaching the 'success' criteria. These 'success' criteria consisted of three objective criteria that represented 'readiness for extubation'. Use of objective criteria removed the subjectivity of clinicians' opinions regarding 'readiness for extubation' in order to reduce the possibility of bias.

The three objective criteria were:

- a mean airway pressure of <8 cmH₂O **and** a fractional inspired oxygen concentration (FiO_2) ≤ 0.35 , both maintained for six consecutive hours
- followed by successful completion of a SBT.

An enrolled infant who reached these criteria had therefore met the primary outcome of the trial.

5.2 Collection and recording of primary outcome data during The VoluVent Trial

As part of routine clinical care in the trial unit neonatal staff frequently observed the MAP and FiO_2 values displayed on the ventilator screen. Every hour the displayed values were recorded on nursing observation charts that are part of each infant's medical records. These values were recorded by the neonatal nurses at approximately the start of every hour and, if possible and appropriate, at a time when the infant was in a resting state in accordance with routine unit practice. In accordance with The VoluVent Trial protocol, these data were also recorded on specifically designed trial data collection sheets by nursing staff caring for enrolled infants (Figure 5-1).

However, given that the MAP values displayed on the screen can vary from breath to breath, the values that are recorded may have been influenced by clinical factors related to the infants, by human behavioural factors related to the nursing staff, and by electromechanical aspects of the ventilators.

Examples of clinical factors affecting the displayed value of an infant's MAP include:

- respiratory rate,
- lung compliance.

The exact time at which the value is observed and recorded by nursing staff may be affected by human behavioural factors. Nurses aim to record the values that are displayed on the ventilator at the start of every hour but the precise timing can vary due to:

- the nurse's workload and possible need to care for other infants,
- clinical emergencies related to the enrolled infant or to other infants,
- the previous clinical experience of the nurse caring for the enrolled infant,
- the inter-observer variability that arises when the nurse responsible for the enrolled infant takes his or her rest break and another nurse is temporarily responsible for the enrolled infant.

The electromechanical aspect that may affect the value recorded by nursing staff relates to the analogue-to-digital conversion of the MAP. Personal correspondence with the company (Carefusion, Yorba Linda, CA) revealed that the MAP value displayed on the ventilator screen is a moving average value averaged over 60 seconds. Therefore, the MAP value may change slightly from one moment to the next and the value recorded by the nurse will depend on the moving average value displayed on the screen at any one time.

Therefore this ancillary study was undertaken to test the validity of data collection used for the primary outcome. A flow chart summarising the study is shown in Figure 5-2.

5.3 Objective

To compare the MAP value that is recorded manually every hour by neonatal nurses, and used as part of the primary outcome for The VoluVent Trial, with electronically sampled MAP values generated with each breath.

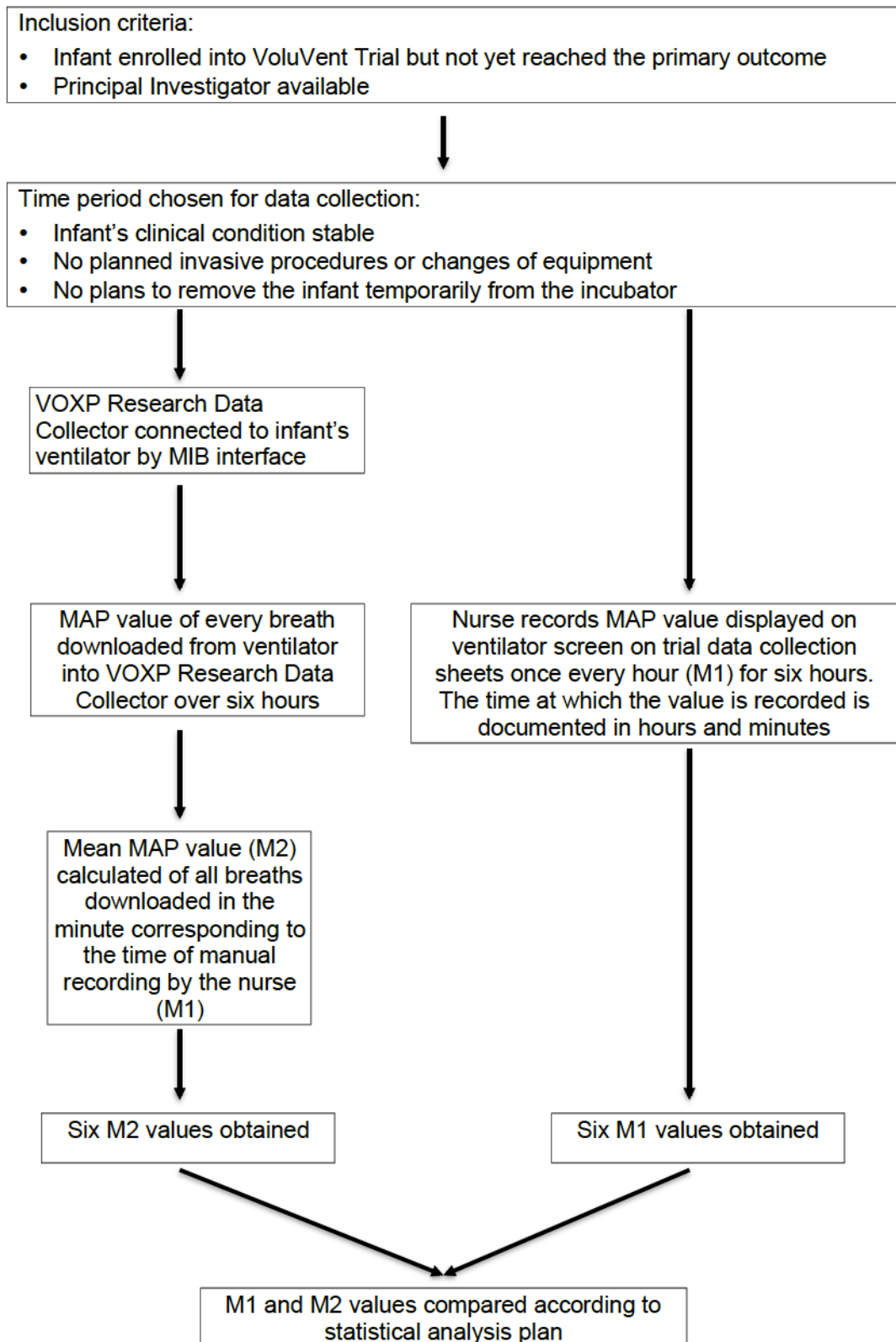


Figure 5-2 Flow chart summarising data collection methods for this ancillary study

5.4 Methods

5.4.1 Inclusion and exclusion criteria

Infants were included in this ancillary study if they had been enrolled into The VoluVent Trial but had not yet met the primary outcome. Selection of infants depended on the availability of the Principal Investigator and therefore infants were not randomly selected for this study. Infants were excluded from this study if the Principal Investigator was not available to set up the device used to sample continuous data produced by the ventilator.

5.4.2 Devices used

Data were downloaded from the ventilators in real time using the VOXP Research Data Collector (Applied Biosignals, GmbH, Germany) software programme installed onto an encrypted laptop computer. This software programme allows researchers to download and store real-time numerical and waveform pulmonary data from AVEA[®] ventilators. The license for use of the software was provided by Applied Biosignals (GmbH, Germany). For this study, the numerical values of MAP generated with every breath were downloaded in real time into Excel spreadsheets generated by the software and stored within the laptop.

MATLAB (MATLAB 2012a, The MathWorks, Inc., Natick, Massachusetts, United States) was used to calculate a 'moving average' of the airway pressure based on the sampled airway pressure data obtained using the VOXP Research Data Collector.

5.4.3 Sampling techniques and data acquisition

Figure 5-3 shows a simplified diagram demonstrating how the infant's airway pressure is detected as a signal by the flow sensor (which contains a hot-wire anemometer) attached to the ETT, transduced and transferred to the ventilator, and displayed on the ventilator screen as a numerical value.

The VOXP Research Data Collector software was used to download data from the AVEA[®] ventilators via a Medical Information Bus (MIB) interface. This allowed continuous airway pressure signals to be sampled and transferred to the software as discrete numerical data within the encrypted laptop computer.

As shown in Figure 5-3, the airway pressure signal (detected by the flow sensor as waveforms) underwent analogue-to-digital conversion before being processed and combined with other variables, and then displayed on the screen as a numerical mean airway pressure value (a moving average over 60 seconds).

Prior to being converted from an analogue to a digital signal the airway pressure signal was sampled by the VOXP Research Data Collector software at an analogue-to-digital rate of 100Hz using a baud rate of 115200. This meant that infant's continuous airway pressure signal was sampled and converted to a discrete numerical value at a rate of 100 times per second.

The software also allows researchers to set the interval at which the variable of interest is downloaded as a numerical value. For this ancillary study an interval of 'every breath' was set so that the software downloaded the MAP with every breath. This 'breath-by-breath' interval was chosen because it ensured that MAP values were sampled as accurately as possible in infants who were spontaneously breathing with variable respiratory rates.

5.4.4 Manual data recording and storage

Values of MAP recorded manually by nursing staff were recorded on nursing observation charts and on specifically designed trial data collection sheets (Figure 5-1). One value was recorded every hour. The nurses used a clock within the neonatal unit to document the time at which the value was recorded. The time was documented in hours and minutes (for example, 10:12, 09:58, 14:06, etc).

5.4.5 Continuous data recording and storage

Data on individual patients were downloaded into Microsoft Excel spreadsheets generated by the VOXP Research Data Collector. Each spreadsheet was saved under each infant's VoluVent Trial number. The electronic data were stored in accordance with South Tees Hospitals NHS Foundation Trust's standard operating procedures (South Tees Hospitals NHS Foundation Trust Information Governance Department, 2007).

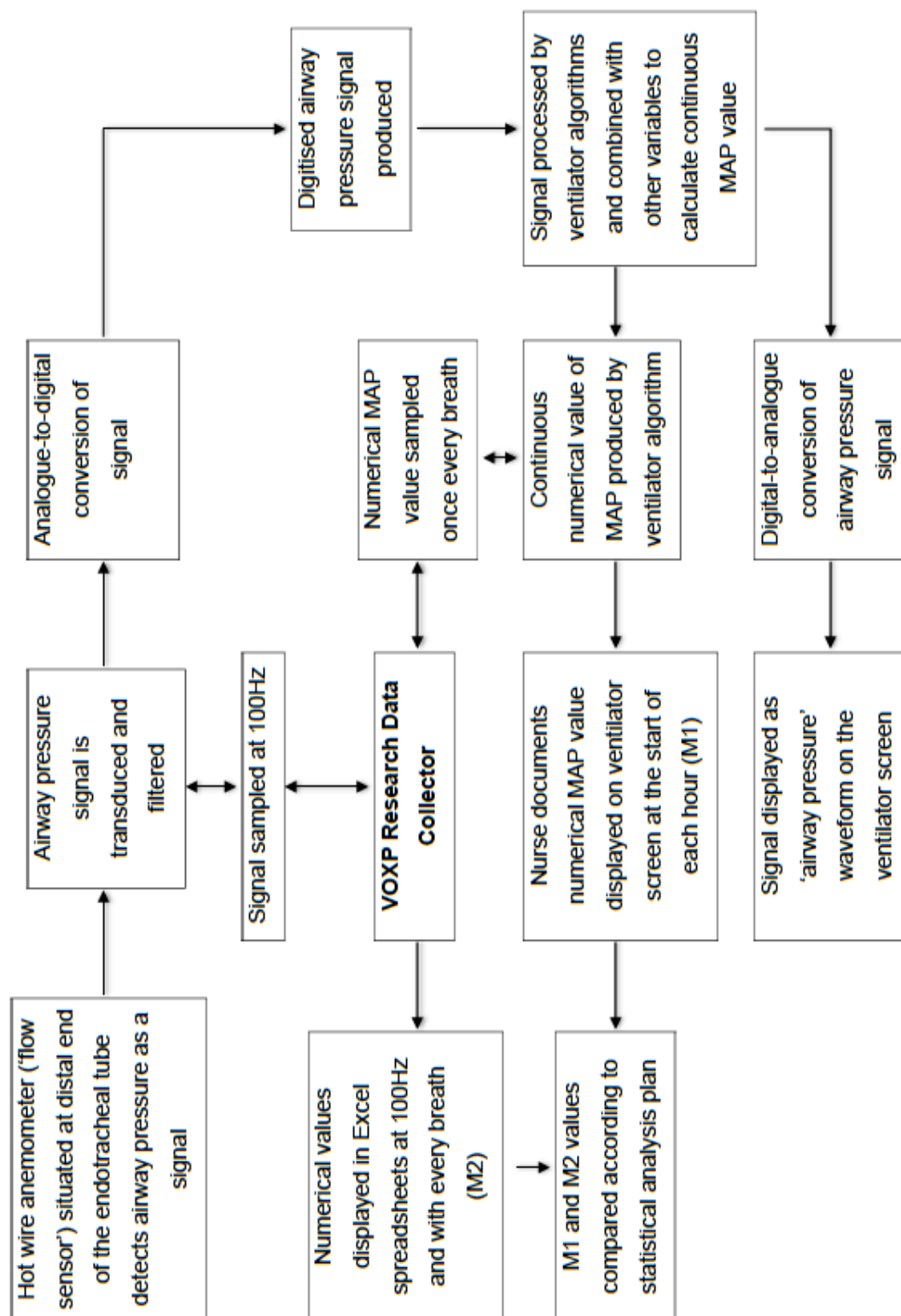


Figure 5-3 Flow chart demonstrating the detection and processing of the airway pressure signal and the sampling and recording of the mean airway pressure values

5.4.6 Time periods of data collection

The focus of this study was to test the validity of the primary outcome by means of comparing two methods of clinical measurement. Therefore data sampled from the ventilator and manual data were collected simultaneously for each infant in this ancillary study. Data were collected at a time when the Principal Investigator was available to set up and close down the VOXP Research Data Collector. The time periods were chosen if the following criteria were met:

- the infant was in a stable clinical condition,
- there were no planned invasive procedures or routine changes of equipment,
- there were no plans to temporarily remove the infant from the incubator.

Routine nursing procedures, including nappy changes and ETT suction, were undertaken according to clinical need.

5.5 Planned statistical analysis

5.5.1 Defining the measurements for comparison of MAP values

M1 value: an MAP value was recorded manually by a nurse once every hour. The time at which this value was recorded was also documented. This was referred to as measurement 1 (M1). The time was recorded as the hour and minute at which the value was documented on the trial data collection sheets (Figure 5-1).

M2 value: MAP values were downloaded by the VOXP Research Data Collector on a breath-by-breath interval. Therefore there were many MAP values that corresponded to the hour and minute at which the M1 value was recorded. The median of all the values downloaded by the VOXP Research Data Collector within the same minute as M1 was calculated and referred to as M2. Initially the SAP stated that the mean value of all MAP values downloaded at breath-by-breath intervals was planned for use as the M2 measurement. However, calculating mean values produced M2 values with decimal points whereas all M1 values were integers. Therefore, the median value was used as the M2 value when compared with M1.

However, several M3 values had decimal places. Therefore, when M2 data were compared with M3 data, the mean values were calculated and compared.

M3 value: sampling the continuous airway pressure signal at 100Hz provided 6,000 airway pressure values per minute. These values were retrospectively converted back to airway pressure waveforms using MATLAB software. A 'moving average' MAP value was calculated from these data. This was done to provide a third measurement (M3) in order to verify the 'breath-by-breath' data (M2). This was done as part of process evaluation of this ancillary study (Moore et al., 2015).

5.5.2 Statistical methods for comparing the two measurements of mean airway pressure

M1 and M2 were compared using the statistical methods for assessing agreement between two methods of clinical measurement described by Bland et al. (Bland et al., 1986). M2 and M3 values were then compared using the same methods in order to verify the M2 measurement.

5.5.3 Comparison of M1 and M2 for one infant only:

The differences between M1 and M2 at each time point were calculated. The overall mean difference \pm two standard deviations (SD) were then calculated (see Table 5-1). As described by Bland et al. (Bland et al., 1986) the upper limit of agreement reflected the mean difference plus two SDs. The lower limit of agreement was the mean difference minus 2 SDs.

Using a Bland Altman plot the difference between M1 and M2 for each time point were plotted against the overall mean difference and the upper and lower limits of agreement. The standard errors (SE) and CIs of the limits of agreement between M1 and M2 were calculated to demonstrate the precision of the limits of agreement.

Hour of data collection	Time (hours and minutes)	MAP value recorded manually every hour (M1), cmH ₂ O	Median MAP value downloaded with every breath (M2), cmH ₂ O	M1 – M2, cmH ₂ O	Mean of M1 plus M2, cmH ₂ O
1					
2					
3					
4					
5					
6					
7					
8					
Sum of M1 – M2, cmH ₂ O					
Mean of M1 – M2, cmH ₂ O					
Mean of M1 – M2 plus 2SD, cmH ₂ O					
Mean of M1 – M2 minus 2SD, cmH ₂ O					

Table 5-1 Example of table comparing repeated values of M1 and M2 for one infant

5.5.4 Comparison of M1 and M2 for several infants

The methods described above were used to compare repeated measurements from several infants. The median value of all of the M1 values from an individual infant was referred to as MedianM1. The median value of all of the M2 values from an individual infant was referred to as MedianM2. The differences between MedianM1 and MedianM2 were plotted against their mean and corrected SD (see Table 5-2). Ninety five per cent of the differences should be between the two corrected SDs to show a good level of agreement between the two methods of measurement (M1 and M2) (Bland et al., 1986).

Participating infant	Median of M1 (MedianM1), cmH ₂ O	Median of M2 (MedianM2), cmH ₂ O	MedianM1 – Median M2, cmH ₂ O	Mean of MedianM1 plus MedianM2, cmH ₂ O
1				
2				
3				
4				
5				
6				
7				
...14				
Total of (MedianM1 – MedianM2), cmH ₂ O				
Mean of (MedianM1 – MedianM2), cmH ₂ O				
Mean of (MedianM1 – MedianM2) plus 2SD, cmH ₂ O				
Mean of (MedianM1 – MedianM2) minus 2SD, cmH ₂ O				

Table 5-2 Example of table comparing repeated median values of M1 and M2 for 14 infants

5.5.5 Verification of M2

The value of M2 was verified using the airway pressure values sampled at 100Hz. Twelve thousand airway pressure values (6000 per minute or 100 times per second, corresponding to 100Hz) were obtained during the minute preceding, and the minute corresponding to, the time at which the nurse recorded the M1 measurement. MATLAB (MATLAB 2012a, The MathWorks, Inc., Natick, Massachusetts, United States) was used to calculate the average value of the 12,000 airway pressure values. This average value was then plotted for every 100th of a second to create a 'moving average'. This also had

the effect of filtering the data to remove artifacts. The mean value of these filtered data was then calculated and referred to as M3. It was compared with M2 using the Bland Altman analysis (Bland et al., 1986).

5.5.6 Recording the timing of the data

At the start of the data collection period for each infant the Principal Investigator recorded the time in hours and minutes using a clock in the neonatal unit. The nurses used the same clock to record the timings of their M1 values in hours and minutes on the specifically designed data collection sheets. The start time documented by the Principal Investigator corresponded to time 00:00, the time recorded in the VOXP Research Data Collector software programme at the start of data collection.

The software programme then continuously recorded the time in hours, minutes, seconds and one tenth of each second (eg: 00:44:29.5 for 44 minutes, 29.5 seconds) throughout the entire period of data collection. The timings documented by the nurses were retrospectively matched to the corresponding time (in hours and minutes) in the Microsoft Excel spreadsheets produced by the software programme. In that way, the MAP values that comprised the M2 and M3 measurements could be matched to the M1 value documented at the same hour and minute by the nurse.

For example, if the start time of the data collection period was recorded as 13:30 and the nurse documented the first M1 value at 13:51, this M1 value was therefore documented 21 minutes after the start of the data collection. This corresponded to data downloaded by the VOXP Research Data Collector 21 minutes after time 00:00. The MAP values downloaded within the 21st minute of data collection (ie: from 00:21.0 to 00:21.9) comprised the M2 values.

5.6 Results

In total, data from 15 infants were collected using the VOXP Research Data Collector. Data from one infant were not subsequently analysed because an M1 value was found to be missing for the 10th hour of data collection. This M1 value had not been documented by the nurse. Therefore, this infant's dataset was not complete. As this ancillary study was an observational study, this infant's data were not analysed.

Of the remaining 14 infants, five were female and nine were male. Six had been randomised to VG and eight to VCV. Their gestational ages ranged from 23 to 28 completed weeks of gestation and their birth weights ranged from 620g to 1317g

The duration of data collection for each of these 14 infants varied from four hours to 15 hours. This variation was primarily due to the availability of the Principal Investigator. Data were collected both during the day and at night. Table 5-4 shows the variation in the duration of data collection for the 14 infants.

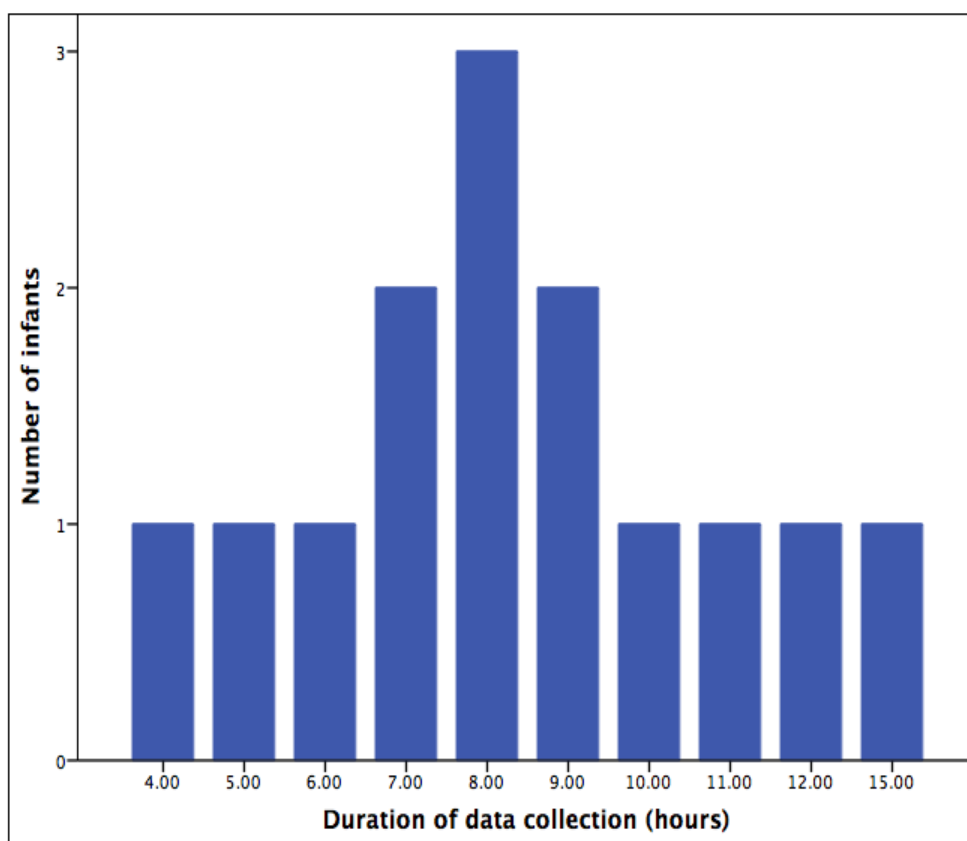


Figure 5-4 Number of hours of data collection for each infant

This graph shows the duration of time over which data were collected for this ancillary study. The shortest duration was four hours and the longest was 15 hours. The most frequent duration was eight hours (three infants).

5.6.1 Example of the Comparison of M1 and M2 (Infant 12)

An example of the data for comparison of M1 and M2 from one of the 14 infants is shown in Table 5-3. For the purpose of this ancillary study this infant is referred to as Infant 12 although that was not his/her actual trial number.

Hour of data collection	Time (hours and minutes)	Value recorded manually every hour (M1), cmH ₂ O	Median value sampled with every breath (M2), cmH ₂ O	M1 – M2, cmH ₂ O	Mean of M1 plus M2, cmH ₂ O
1	09:55	9	9	0	9
2	11:10	8	8	0	8
3	12:00	8	10	-2	9
4	13:10	10	11	-1	10.5
5	14:05	10	11	-1	10.5
6	15:10	8	9	-1	8.5
7	16:10	9	9	0	9
8	17:15	8	7	1	7.5
Sum of M1 – M2, cm H ₂ O				-4	
Mean of M1 – M2, cm H ₂ O				-0.5	
Mean of M1 – M2 plus 2SD, cm H ₂ O				1.352	
Mean of M1 – M2 minus 2SD, cm H ₂ O				-2.352	

Table 5-3 Example of comparison of M1 and M2 data for Infant 12

5.6.2 Bland Altman plot for Infant 12

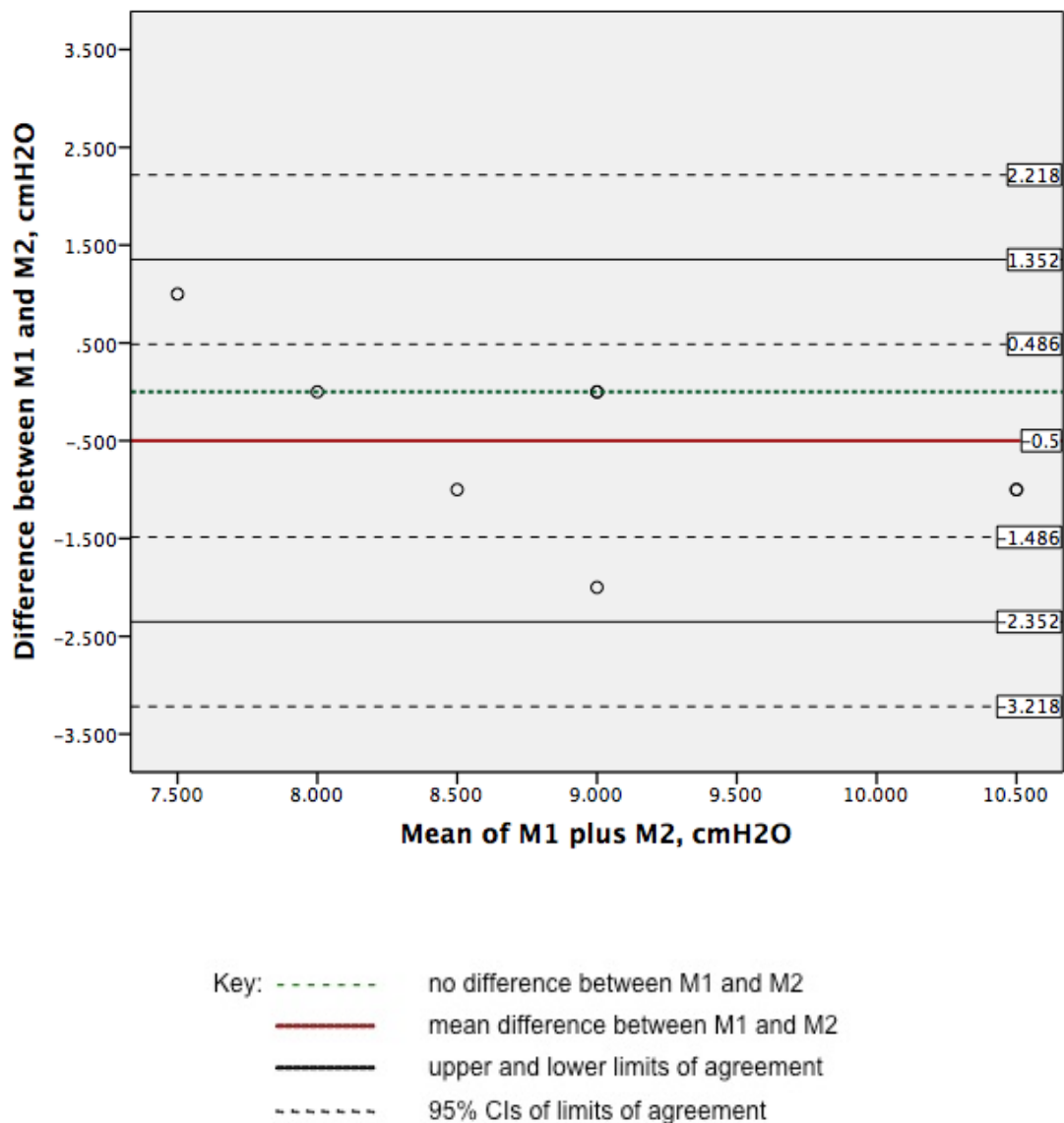


Figure 5-5 Bland Altman plot showing the differences between M1 and M2 and their variance from the overall mean difference over eight consecutive time points for Infant 12.

5.6.3 Description of the Bland Altman plot comparing M1 and M2 for Infant 12

- The mean difference between M1 and M2 for this infant was -0.5 cmH₂O.
- The upper limit of agreement was the mean of M1 and M2 plus 2 SDs. In this case, this upper limit of agreement was 1.352 cmH₂O.
- The lower limit of agreement was the mean of M1 and M2 minus 2 SDs, which, for this infant, was -2.352 cmH₂O.
- The standard error of the mean difference +/- two SDs was 0.567. Therefore the 95% CIs of the upper limit of agreement were 0.486 to 2.218 cmH₂O. The 95% CIs of the lower limit of agreement were -1.486 to -3.218 cmH₂O.

M1 was used as the reference against which M2 was compared. For this infant, there were no differences between three of the eight measurements at hours 1, 2 and 7. At the eighth hour the MAP value documented by the nurse (M1) was 1 cmH₂O higher than the median MAP value downloaded with every breath (M2) at the same time period. At hours 4, 5 and 6, M1 was 1 cmH₂O lower than M2. At the third hour, M1 was 2 cmH₂O lower than M2. This created a negative overall mean difference of -0.5 cmH₂O.

5.6.4 Explanation of the Bland Altman plot comparing M1 and M2 for Infant 12

For Infant 12, the mean difference between the MAP value documented by the nurse every hour (M1) and the median MAP value downloaded from the ventilator with every breath (M2) at the same time point was -0.5 cmH₂O. The value documented by the nurse tended to be lower than the value downloaded by the VOXP Research Data Collector, giving the mean difference a negative value.

At each time point, the difference between the values of M1 and M2 falls within the upper and lower limits of agreement (the mean difference +/- two SDs). Therefore, for Infant 12, this indicates good agreement between the two measurements.

5.6.5 Comparison of M1 and M2 for all 14 infants

Infant	Median of M1 (MedianM1), cmH ₂ O	Median of M2 (MedianM2), cmH ₂ O	MedianM1 – MedianM2, cmH ₂ O	Mean of MedianM1 plus MedianM2, cmH ₂ O
1	9	9	0	9
2	7	7	0	7
3	7	7	0	7
4	6	6.5	-0.5	6.25
5	8	8	0	8
6	9	9	0	9
7	6.5	7	-0.5	7.75
8	8	8	0	8
9	8	8	0	8
10	9	9	0	9
11	9	9	0	9
12	8.5	9	-0.5	8.75
13	8	8	0	8
14	7	7	0	7
Total of (MedianM1 – MedianM2), cm H ₂ O			-1.5	
Mean of (MedianM1 – MedianM2), cm H ₂ O			-0.11	
Mean of (MedianM1 – MedianM2) plus 2SD, cm H ₂ O			0.316	
Mean of (MedianM1 – MedianM2) minus 2SD, cm H ₂ O			-0.536	

Table 5-4 Comparison of M1 and M2 data for 14 infants

5.6.6 Bland Altman plot for the comparison of M1 and M2 for all 14 infants

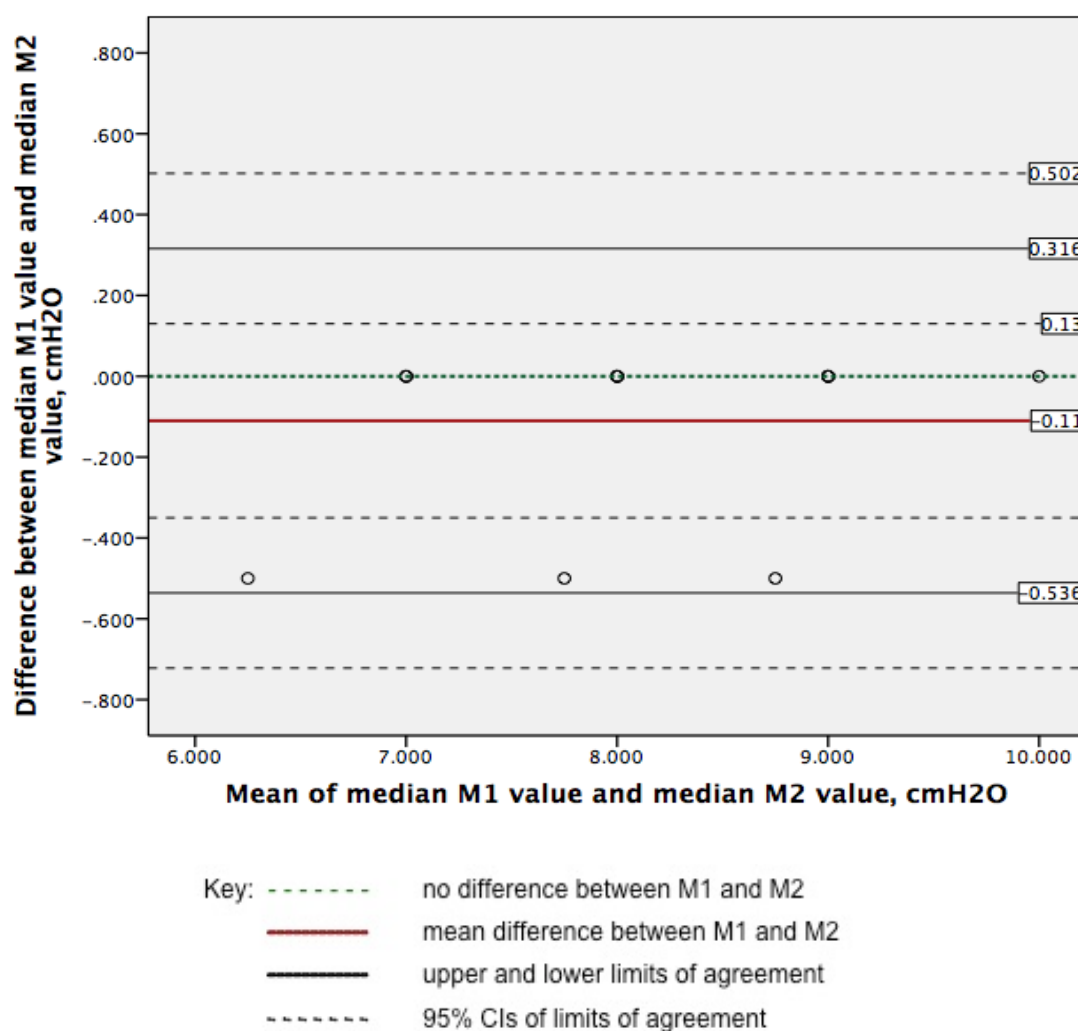


Figure 5-6 Bland Altman plot showing how the differences between MedianM1 and MedianM2 differ from the overall mean difference for all 14 infants.

5.6.7 Description of the Bland Altman plot comparing M1 and M2 for all 14 infants

- The mean difference between MedianM1 and MedianM2 for all infants was -0.11 cmH₂O.
- The upper limit of agreement was the mean of MedianM1 and MedianM2 plus 2 SDs. The upper limit of agreement was calculated as 0.316 cmH₂O for all 14 infants.
- The lower limit of agreement was the mean of MedianM1 and MedianM2 minus 2 SDs, which, for all infants, was -0.536 cmH₂O.
- The standard error of the mean difference +/- two SDs was 0.099. Therefore the 95% CIs of the upper limit of agreement were 0.13 to 0.502 cmH₂O. The 95% CIs of the lower limit of agreement were -0.722 to -0.35 cmH₂O.

For 11 of the 14 infants, there was no difference between the MedianM1 and MedianM2 values. For three of the infants, the MedianM1 value was 0.5 cmH₂O lower than the MedianM2 value.

5.6.8 Explanation of the Bland Altman plot comparing M1 and M2 for all 14 infants

For all 14 infants, the mean difference between the median M1 values (MedianM1) and the median M2 values (MedianM2) at the same time points was -0.11 cmH₂O. For three infants, the value documented by the nurse was 0.5 cmH₂O lower than the value downloaded by the VOXP Research Data Collector, resulting in this negative mean difference.

The differences between the values of MedianM1 and MedianM2 all fell within the upper and lower limits of agreement (the mean difference +/- two SDs) and well within the 95% CIs of these limits of agreement. Therefore this demonstrates very good agreement between the two measurements when the median values for all 14 infants are compared.

5.6.9 Verification of M2

Two sets of data obtained using the VOXP Research Data Collector were analysed for this study. One set comprised the mean airway pressure values sampled with every breath (M2), as analysed above. The other set comprised more sensitive data used to verify the M2 data. These other data consisted of

the airway pressure values sampled 100 times per second and downloaded into a separate Microsoft Excel file created by the VOXP Research Data Collector. The VOXP Research Data Collector downloaded these data, as well as the M2 data, simultaneously.

These data were used to create a visual display of the 12,000 airway pressure data values downloaded during the minute preceding, and the minute corresponding to, the M1 value. An average airway pressure value was also calculated and referred to as M3. This was done using MATLAB software (MATLAB 2012a, The MathWorks, Inc., Natick, Massachusetts, United States). As shown in Figure 5-7, the visual display resembled the airway pressure graphic waveforms commonly displayed on modern ventilators.

In Figure 5-7 the time of the data collection is on the x-axis and the airway pressure is on the y-axis. The 12,000 data points obtained using the VOXP Research Data Collector were used to create the airway pressure waveform graphic shown in blue in the figure. The red line represents the 'moving average' of all of these data points. The red number on the right side of the figure represents the mean value of all of these data points. This value is the M3 value and, for this infant, was 7 cmH₂O

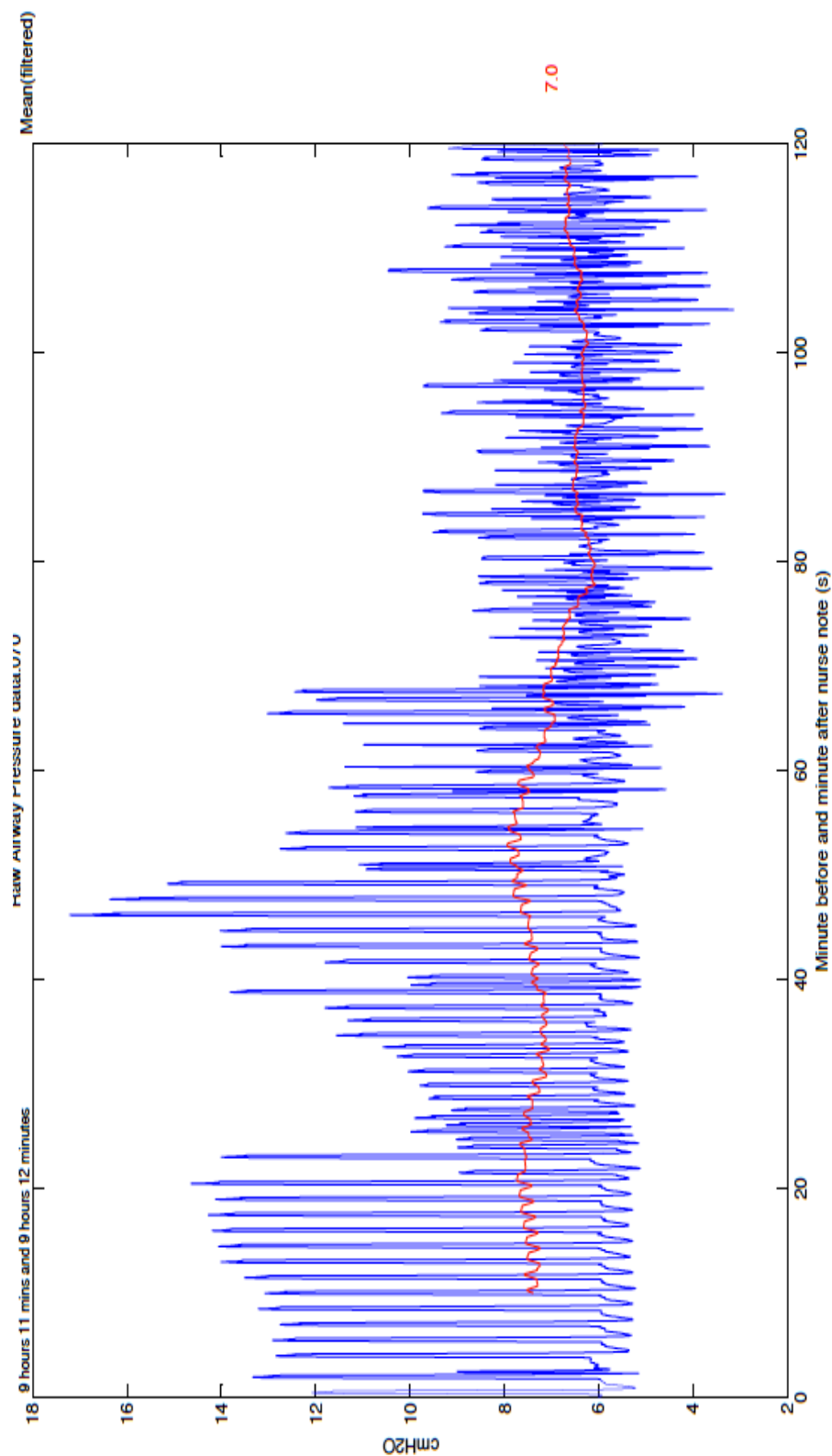


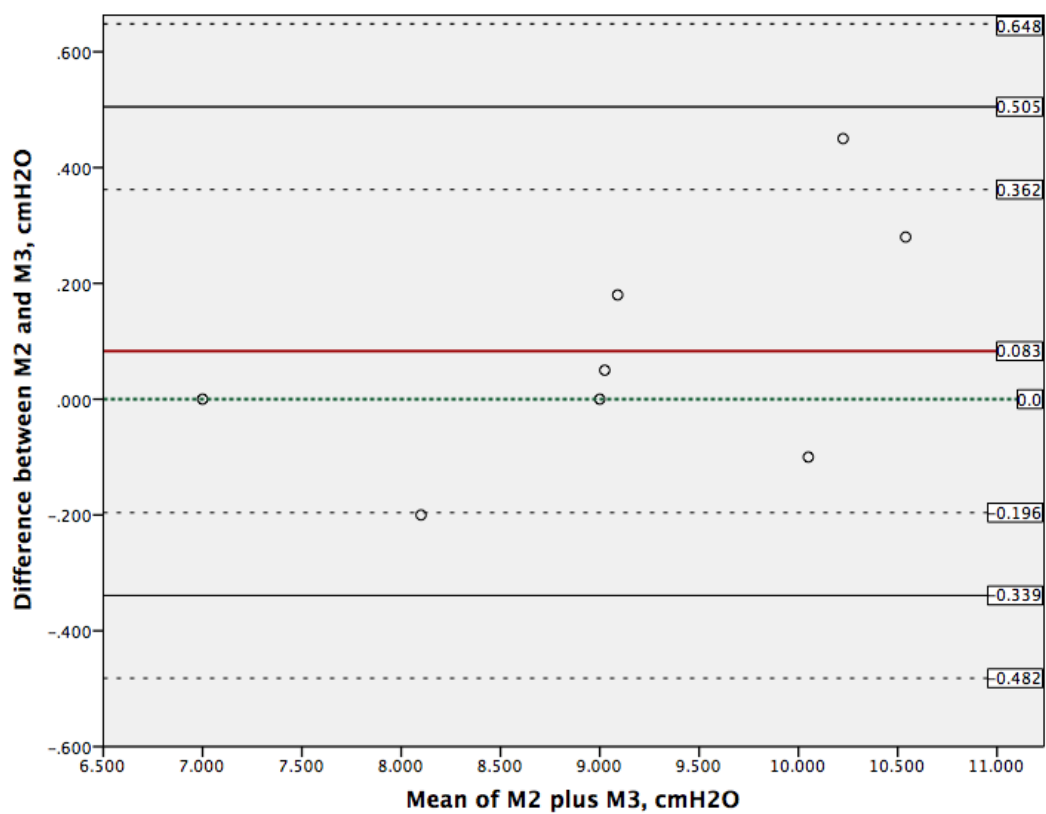
Figure 5-7 Output from MATLAB software when analysing M3 data for one infant (analysed and produced by Ms Audrey Wilkinson, Northern Medical Physics and Clinical Engineering)

5.6.10 Results of comparison of M2 and M3 values

Data from 12 of the 14 infants in this study were used to verify the M2 data. M3 data on two infants were not available for comparison. M2 was used as the comparison against which M3 was compared. Table 5-5 shows an example of these data from Infant 12.

Hour of data collection	Time (hours and minutes)	Mean of M2, cmH ₂ O	Mean of M3, cmH ₂ O	M2 – M3, cmH ₂ O	Mean of M2 plus M3, cmH ₂ O
1	09:55	9	9	0	9
2	11:10	8	8.2	-0.2	8.1
3	12:00	10	10.1	-0.1	10.05
4	13:10	10.68	10.4	0.28	10.54
5	14:05	10.45	10	0.45	10.225
6	15:10	9.05	9	0.05	9.025
7	16:10	9.18	9	0.18	9.09
8	17:15	7	7	0	7
Sum of M2 – M3, cmH ₂ O				0.66	
Mean of M2 – M3, cmH ₂ O				0.083	
Mean of M2 – M3 plus 2SD, cmH ₂ O				0.505	
Mean of M2 – M3 minus 2SD, cmH ₂ O				-0.339	

Table 5-5 Example of comparison of M2 and M3 data from Infant 12



Key:
 - - - - - no difference between M1 and M2
 ——— mean difference between M1 and M2
 ——— upper and lower limits of agreement
 95% CIs of limits of agreement

Figure 5-8 Bland Altman plot showing the comparison of M2 and M3 data for Infant 12

5.6.11 Description of the Bland Altman plot comparing M2 and M3 for Infant 12

- The mean difference between M2 and M3 for this infant was 0.083 cmH₂O.
- The upper limit of agreement was the mean of M2 and M3 plus 2 SDs. In this case, this upper limit of agreement was 0.505 cmH₂O.
- The lower limit of agreement was the mean of M2 and M3 minus 2 SDs, which, for this infant, was -0.339 cmH₂O.
- The standard error of the mean difference +/- two SDs was 0.567. Therefore the 95% CIs of the upper limit of agreement were 0.362 to 0.648 cmH₂O. The 95% CIs of the lower limit of agreement were -0.196 to -0.482 cmH₂O.

M2 was used as the reference against which M3 was compared. For this infant, there was no difference between two of the eight measurements at hours 1 and 8. The biggest difference between the two measurements occurred at hour 5 when the M2 value was 0.45 cmH₂O higher than that of M3. At hours 4 to 7, the M2 value was higher than that of M3. At hours 2 and 3, the M3 value was higher than that of M2. Therefore, more of the differences were positive than negative.

5.6.12 Explanation of the Bland Altman plot comparing M2 and M3 for Infant 12

For Infant 12, the mean difference between M2 and M3 was 0.083 cmH₂O. At each time point, the difference between the values of M2 and M3 fell within the upper and lower limits of agreement (the mean difference +/- two SDs). Therefore, for Infant 12, this indicates good agreement between the two measurements.

5.6.13 Comparison of MeanM2 and MeanM3 for 12 of the 14 infants

Table 5-6 shows the comparison of the mean values of M2 and M3 for 12 of the 14 infants, with M2 as the reference value. M3 data on Infants 1 and 8 were not available.

Subject	Mean of M2 (MeanM2), cmH ₂ O	Mean of M3 (MeanM3), cmH ₂ O	MeanM2 – MeanM3, cmH ₂ O	Mean of MeanM2 plus MeanM3, cmH ₂ O
2	6.93	6.86	0.07	6.895
3	7.18	7.22	-0.04	7.2
4	6.37	6.36	0.01	6.365
5	7.8	7.82	-0.02	7.81
6	8.88	8.86	0.02	8.87
7	6.74	6.55	0.19	6.645
9	7.65	7.64	0.01	7.645
10	8.9	8.84	0.06	8.87
11	8.71	8.81	-0.1	8.76
12	9.17	9.09	0.08	9.13
13	7.84	7.84	0	7.84
14	7.07	7.14	-0.07	7.055
Total of (MeanM2 – MeanM3), cmH ₂ O			0.21	
Mean of (MeanM2 – MeanM3), cmH ₂ O			0.018	
Mean of (MeanM2 – MeanM3) plus 2SD, cmH ₂ O			0.172	
Mean of (MeanM2 – MeanM3) minus 2SD, cmH ₂ O			-0.136	

Table 5-6 Comparison of MeanM2 and MeanM3 data for 12 infants

5.6.14 Bland Altman plot for the comparison of M2 and M3 for 12 of the 14 infants

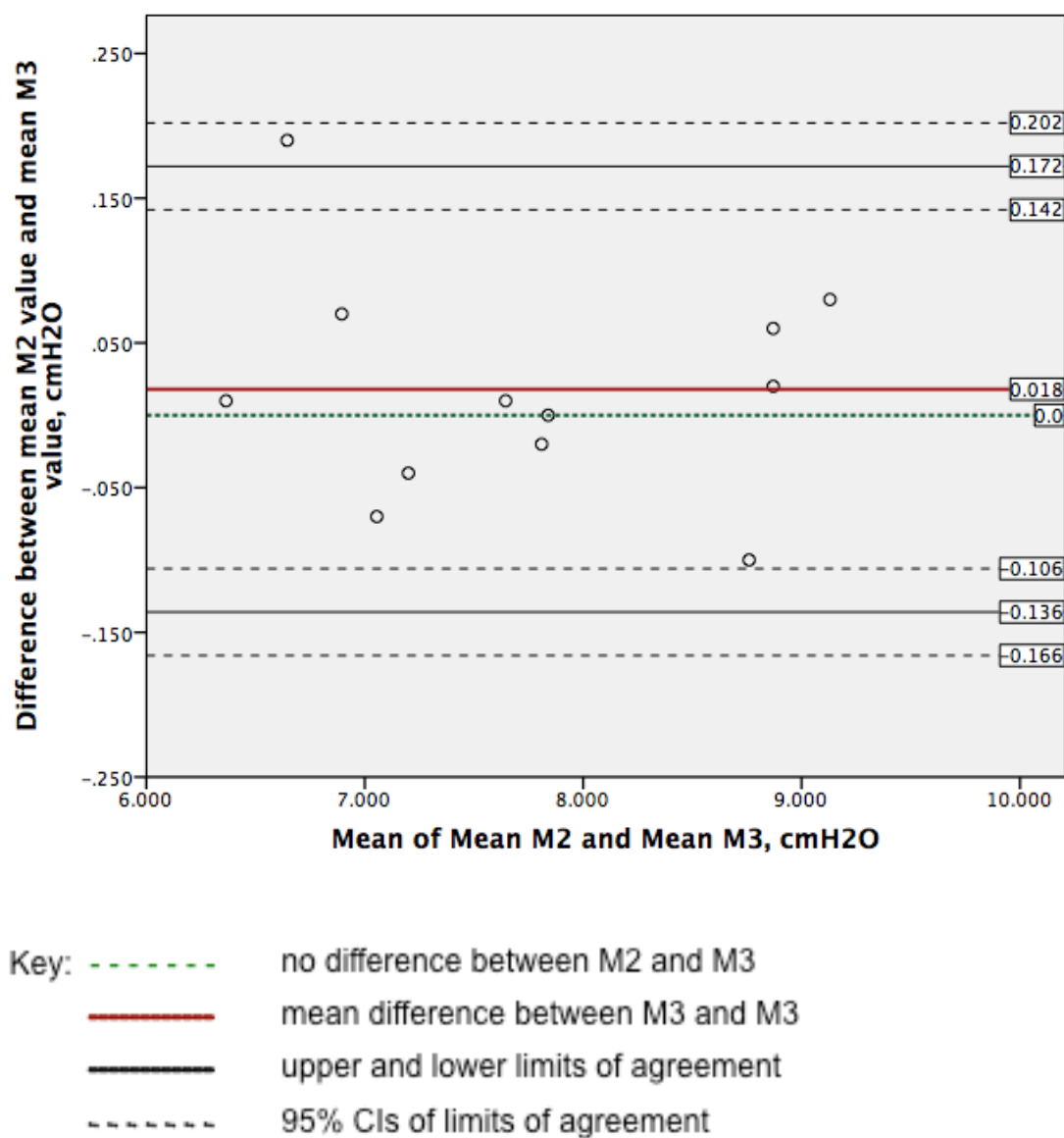


Figure 5-9 Bland Altman plot for the comparison of MeanM2 and MeanM3 values for 12 infants

5.6.15 Description of the Bland Altman plot comparing M2 and M3 for 12 infants

- The mean difference between MeanM2 and MeanM3 for 12 infants was 0.018 cmH₂O.
- The upper limit of agreement was the mean of MeanM2 and MeanM3 plus 2 SDs. The upper limit of agreement was calculated as 0.172 cmH₂O for 12 infants.
- The lower limit of agreement was the mean of MeanM2 and MeanM3 minus 2 SDs, which, for these 12 infants, was -0.136 cmH₂O.
- The standard error of the mean difference +/- two SDs was 0.039. Therefore the 95% CIs of the upper limit of agreement were 0.142 to 0.202 cmH₂O. The 95% CIs of the lower limit of agreement were -0.106 to -0.166 cmH₂O.

For one of the 12 infants, there was no difference between the MeanM2 and MeanM3 values. The largest difference between M2 and M3 was 0.19 cmH₂O (Infant 7). All other differences were ≤ 0.07 cmH₂O.

5.6.16 Explanation of the Bland Altman plot comparing M2 and M3 for 13 infants

The Bland Altman plot demonstrates good agreement between the two measurements when the mean values for 12 infants were compared. The only difference that fell outside the limits of agreement for the mean difference was that of Infant 7. However, this mean difference was still within the upper 95% CI of the upper limit of agreement.

Therefore, based on these data, M2 values were verified with the M3 measurements.

5.7 Strengths and limitations of this ancillary study

There are several strengths and limitations of this ancillary study. These are discussed below.

5.7.1 Strengths

- The aim of this ancillary study was to validate one of the three 'success criteria' used as the primary outcome for The VoluVent Trial. This is an important part of complex interventions research, particularly in a trial such

as this in which the primary outcome measure is documented by a variety of nurses in a busy intensive care unit. The M1 and M2 measurements showed good agreement, demonstrating that the MAP values documented by nursing staff once every hour were representative of the MAP values generated with every breath.

- In this ancillary study two methods of clinical measurement were compared, the manual recording of MAP once every hour (M1) and the sampling of an MAP value with every breath using computer software (M2). M2 was also verified by M3 data. This is the first study to make these comparisons in ventilated infants. It validated the primary outcome and also provided useful information for routine clinical care in NICU. It demonstrated that hourly documentation of MAP by nursing staff is a good reflection of the MAP values generated throughout each hour. This indicates that manual recordings are as good as electronic data.
- The VOXP Research Data Collector uses software that samples a signal at 100Hz. This meant that the airway pressure was sampled 100 times per second. In order to sample a continuous signal at an adequate rate to detect changes in that signal, Nyquist sampling theorem states that the sampling frequency should be twice as high as the frequency in the signal (Olshausen, 2000). The frequency of an airway pressure signal is complex and should be sampled many times per second to obtain adequately sensitive data. A sampling rate of 100Hz was sufficient to obtain digital data (airway pressure values every 100th of a second) and use it to recreate the airway pressure waveforms graphically. This sampling rate produced data that provided sensitive M3 values which were not difficult to store electronically. The software was also used on a standard laptop computer. This approach to a study involving signal analysis, nested within an intensive care RCT, is a useful part of process evaluation in a complex interventions trial (Moore et al., 2015).

5.7.2 Limitations

- Data could only be collected when the Principal Investigator was available to set up the VOXP Research Data Collector to collect data from the ventilators in 'real time'. Therefore infants were not selected in a truly randomised

fashion. However, the only determinant of infant selection was the availability of the Principal Investigator. No other aspect of the infant's care, condition or participation in The VoluVent Trial was taken into account. The Principal Investigator was not required to be present during the period of data collection. Data collection was continued for as long as possible. However availability of the Principal Investigator did determine the duration of data collection for each infant because she also had to be available to stop the data collection.

- The use of a clock to record the timings of data collection may have limited the data. The nurses recorded the times at which M1 values were documented as accurately as possible to the nearest minute. The use of a clock may have introduced an element of subjectivity in these timings. The VOXP Research Data Collector used a timer built into its software. The Principal Investigator retrospectively matched the M1 data with those comprising the M2 and M3 data. Although this was done as accurately as possible, the use of two different timers may have affected the reliability of matching the data. A means of improving this would be to use a timer that the nurses can use for the M1 data that is calibrated before each use and synchronised with the timer in the VOXP Research Data Collector. This would improve the accuracy of the matching of data.
- The duration of data collection may have affected the reliability of the data obtained for some of the infants. Data for Infant 8 was collected over four hours. Therefore there were only four time points for use during the analysis for this infant. This may explain why this infant appears as a possible outlier in the Bland Altman plot for comparison of M2 and M3 values for 13 infants. However, in the analysis comparing M1 and M2 values this infant does not appear to be an outlier. Therefore, it is not clear from this study whether the duration of data collection affects the reliability of the data.
- Fourteen infants were originally included in this ancillary study and contributed data for the comparison of M1 and M2. However, M3 data from only 12 infants was available for analysis to verify the M2 data. This may have affected the validity of the comparison of M2 and M3 values.
- Data were collected on all 14 infants during routine periods of care within the NICU. The criteria for inclusion of an infant in this ancillary study were:

- a. the infant had to have stable clinical conditions,
- b. no invasive procedures or routine changes of equipment were planned,
- c. temporary removal of the infant from the incubator was not planned.

Whilst these criteria were adhered to, routine care may still have involved some periods of handling or movement of these infants. This may have affected the MAP of these infants at times. During handling the MAP is likely to be more variable than during periods of rest. When infants are awake the MAP may be more variable than during periods of sleep as infants may make more vigorous movements when awake. If the study had been planned so that data were only collected when infants were asleep and not being handled, the variability in MAP data may have been less. However, this can also be considered a strength of the study in that the data collected are a true representation of the MAP generated in ventilated infants in NICU.

- The design of this study meant that the nurses had to know when the data collection periods were taking place. They also had to record the time of documentation of MAP in hours and minutes. This is a deviation from routine practice during which they record the MAP to the nearest hour only. The nurses were also aware of the presence of a laptop connected to the infants' ventilators during the data collection periods. These issues may have introduced observer bias into the study by affecting the nurses' behaviour regarding observation of the MAP on the ventilator screen, documentation of the MAP value, and documentation of timings to the nearest minute.

5.7.3 Conclusion

This ancillary study was undertaken as part of process evaluation of The VoluVent Trial to validate one of the elements of the primary outcome measure. This element was the MAP value documented by nursing staff every hour and used as part of the primary outcome. Although the primary outcome is considered to be a subjective measure, the MAP values can be affected by clinical, human and electromechanical factors.

This study compared the median MAP values manually recorded by nurses every hour during data collection with the median MAP values sampled and

downloaded with every breath at the same time points. Comparison of these two measurements using Bland Altman analysis showed good agreement between the two measurements. This means that the MAP values documented once an hour by the nurses are a good representation of the MAP values being generated with every breath.

According to the SAP for this ancillary study, written prior to data analysis, the proportion of M2 and M3 values between the two corrected SDs was high enough to indicate a good level of agreement between M2 and M3. This means that the M2 measurement was verified by M3.

Chapter 6 Consent for Neonatal Emergency Care Trials

6.1 Introduction

Informed consent forms the cornerstone of research ethics (World Medical Association, 2013). The justification for informed consent in research arose from the Nuremburg Trials, from which the ten ethical principles forming the Nuremburg Code (Doyal et al., 2001a) were created. The fundamental elements of informed consent (Beauchamp et al., 2001) include:

- capacity (on behalf of the person giving consent)
- disclosure (of information about the research study by the researcher or clinician)
- understanding (of that information)
- voluntariness (in giving consent without coercion)
- consent

However, the form that informed consent should take continues to be debated (Doyal et al., 2001b).

The most commonly recognised form of informed consent for research is prospective consent obtained from the eligible individuals themselves (Beauchamp et al., 2001). However, as demonstrated in The VoluVent Trial, prospective consent may not be suitable for all research studies. Deferred consent for research is becoming more widely accepted in the emergency care setting (Crash-2 trial collaborators, 2010; Perkins et al., 2016; Lyttle et al., 2017). However there are still gaps in knowledge about the use of deferred consent in neonatal research. The VoluVent Trial highlighted some of these gaps. They relate to the ethical principles and the practical implementation of deferred consent in a neonatal trial. They also relate to the impact that deferred consent has on the consent procedure and the design of a neonatal trial.

The gaps in knowledge are linked to the unique differences between obtaining consent for research involving adults or older children, and for research involving infants. These differences shall be discussed first, followed by a summary of the impact of deferred consent on The VoluVent Trial with reference to published literature.

6.2 Informed consent in neonatal research

There are many similarities between the elements of informed consent procedures for neonatal and paediatric research, and for adult research. However, there is a fundamental difference between newborn infants and older children or adults. By virtue of their age and physical, cognitive and emotional developmental status, newborn infants lack the capacity to give informed consent. The four components of capacity, as described in the Mental Capacity Act of 2005 (Mental Capacity Act, 2005) are the abilities to:

- understand the information given,
- retain the information given,
- make a decision based on the information given,
- communicate that decision.

None of these components can apply to seeking consent for the participation of newborn infants in research studies. They can apply to older children depending on the age of the child and the circumstances (General Medical Council, 2007). Therefore, in neonatal research, informed consent must always be sought from someone other than the eligible infant. The decision to participate in the neonatal research study is never made by the participant. This is known as proxy consent (Montgomery, 2001). It adds another level of complexity to the informed consent process in neonatal research studies.

6.2.1 Proxy consent

In the United Kingdom, proxy consent can be given by the person or persons with parental responsibility for an infant (Foex, 2001). Other than in exceptional circumstances a newborn infant's mother always has parental responsibility. She can give proxy consent for research at any time provided she has the capacity to give consent (General Medical Council, 2007). An infant's father has parental responsibility if he is married to the infant's mother at the time of birth. Therefore a married father can also give proxy consent for an infant to participate in research.

However an unmarried father only assumes parental responsibility after being named as the infant's father on the birth certificate (Children Act, 2004). Therefore an unmarried father cannot provide consent for neonatal research. In

practice, an unmarried father could sign a consent form for his infant but the mother must also agree to the study and sign the form as she is the only one with parental responsibility at that time. In the United Kingdom same-sex couples both have parental responsibility if they are married or in a civil partnership at the time of conception. If they are not married or in a civil partnership, the parent who did not give birth to the child gains parental responsibility if named on the birth certificate or if a parental responsibility agreement is made (Parental Rights and Responsibilities, gov.uk).

Therefore the law regarding parental responsibility is one of the ways in which seeking consent for neonatal research involves unique challenges. Many infants are now born to unmarried couples. Despite it being good practice to involve both parents in a discussion and decision about neonatal research, only the mother can provide written consent if they are not married.

In The VoluVent Trial an infant was enrolled only if written consent had been obtained from someone with parental responsibility. Mothers and married fathers could give proxy consent provided they had the capacity to do so (Mental Capacity Act, 2005). Unmarried fathers could not give proxy consent as the infants' births had not been registered within the required timeframe.

Throughout this thesis, the term 'consent' refers to proxy consent when it is used in reference to consent from parents (or someone with parental responsibility) on behalf of the newborn infant.

6.2.2 Prospective consent

In research, prospective consent refers to consent obtained before the patient is exposed to any part of a trial protocol. This includes randomisation and exposure to interventions. This is a commonly used form of consent in neonatal research.

6.2.3 Advantages of prospective consent

An important advantage of prospective consent is that it aims to preserve autonomy. In neonatal research, it is parental autonomy that is preserved because it is the parents, not the infant, who are providing consent (Beauchamp and Childress, 2001). It enables parents to make decisions about all aspects of their infant's management in relation to research. Prospective consent is

suitable for any type of non-emergency research. It should be used in non-emergency neonatal research so that parents have the opportunity to make decisions about research at all stages.

6.2.4 Disadvantages of prospective consent

Prospective consent has been, and continues to be, used for emergency interventions research (Azzopardi et al., 2008; Singh et al., 2006). However, it can lead to difficulties with obtaining informed consent that then impact on recruitment rates. These were demonstrated well during the first four months of The VoluVent Trial and will be discussed here.

6.2.4.1 Initial use of prospective consent in The VoluVent Trial

Between July and November 2013, prospective written parental consent was sought according to the original trial protocol (version 7, dated 18th July 2013). Verbal and written information was offered to parents before the birth of their infant if it was possible and appropriate to do so. If not, information was offered after a potentially eligible infant's birth, again only if it was possible and appropriate to do so. Written parental consent had to be obtained within 12 hours of intubation before an infant could be randomised.

Therefore, before obtaining consent, a potentially eligible infant initially received VCV. If parental consent was obtained within 12 hours of intubation the infant was then randomised within the appropriate stratification group. If that infant was randomised to VCV, no changes were made to his or her ventilation. If the infant was randomised to VG, the mode of ventilation was therefore changed to VG.

Obtaining prospective consent for the trial was difficult for a number of reasons. Seventeen sets of parents either declined consent or, in the case of outborn infants, were not present in the hospital within 12 hours of intubation. Although they were not asked for their reasons for declining, several parents voluntarily explained their reasons. Many of these were similar to those reported recently by authors of another neonatal emergency interventions trial (Songstad et al., 2017). These included

- feeling unable to make a decision within 12 hours,

- feeling uncomfortable with the prospect that randomisation may lead to a change in their infant's ventilation,
- feeling unable to consider the information due to fatigue, worry or the effects of medications,
- in the cases of outborn infants, feeling unable to consider the information within the very narrow timeframe because they had only just arrived at the trial site.

On some occasions, members of the clinical or research teams did not approach parents because they felt that the timing was not appropriate. As a result, recruitment was affected with only six infants recruited being in four months.

The challenges described by parents demonstrate clearly that parents are often not in a position to give fully informed consent shortly after the birth of a sick or preterm infant. These challenges, highlighted by the attempted use of prospective consent in an emergency interventions trial, are discussed in more detail below. Some of them are unique to neonatal research.

6.2.4.2 Challenges in using prospective consent in neonatal emergency interventions research

One commonly occurring challenge in neonatal research is that mothers have often received sedation or anaesthesia shortly before the birth of their infants. This may affect their capacity to give consent (Mental Capacity Act, 2005). In The VoluVent Trial half of the trial population were born by caesarean section, meaning that at least half of the mothers would have received anaesthesia or potent analgesia at the time of delivery. In this regard, the context of consent in neonatal emergency interventions research differs from that of non-emergency interventions research. It also differs from paediatric research because most parents of older children are not themselves recovering from childbirth or a major operation.

Therefore the physical effects of labour and childbirth on the mother create a unique challenge in seeking consent for neonatal emergency interventions research. Fatigue, anxiety or distress may also impact on both parents' abilities to give informed consent in the first few hours after their infant's birth (Mason, 1997; Manning, 2000). If the father does not have parental responsibility, this

creates an additional challenge unique to neonatal emergency interventions research.

As highlighted by The VoluVent Trial, parents may feel uncomfortable with the prospect that their decision to give consent may lead to a change in their infant's management through randomisation. This is consistent with published literature (Harron et al., 2015) and emphasises the burden of responsibility that parents may feel in this situation. It is possible that parents would not have the same concerns regarding their own participation in an adult study. In neonatal research, parents have had a shorter relationship with their infants compared with parents of older children eligible for paediatric research. Whilst the duration of this relationship does not determine the strength of parent-infant bond it may impact on parents' decisions regarding consent for neonatal research. These factors all highlight the complex and often unique challenges that arise when considering consent for neonatal emergency interventions research.

One methodological disadvantage with prospective consent in emergency interventions research is that initial management of participants prior to protocol implementation may affect the scientific validity of the trial results. Initially a potential participant may receive one particular type of intervention before consent is obtained. After consent is obtained and randomisation occurs they may then receive a different intervention. Depending on the trial design and the intention-to-treat definition used in the protocol this can impact on the validity and reliability of the results.

These examples demonstrate that, in neonatal emergency interventions research, prospective consent may not be an appropriate method for seeking informed consent.

6.3 Deferred consent

Deferred consent refers to consent given by a patient or a proxy after part of the protocol has already been implemented. The person giving consent therefore gives permission for the intervention or protocol to continue and for the researchers to use the participant's data for the study (Woolfall et al., 2013). Deferred consent has been permissible for children's research studies in the UK since the Clinical Trials Regulations were updated in 2008 (The Medicines for Human Use (Clinical Trials) and Blood Safety and Quality (Amendment)

Regulations, 2008). The regulations specify that certain conditions must exist that render fully informed prospective consent prior to starting the trial protocol impossible. These conditions are that:

- “the minor requires urgent treatment,
- urgent action is required for the purposes of the trial,
- meeting the requirements [in obtaining informed consent] is not reasonably practicable,
- an ethics committee has given its approval”.

Deferred consent is not suitable for all studies but does make good quality research into emergency interventions possible. If deferred consent is declined the participant takes no further part in the study and no data related to that participant are used for purpose of the study.

Deferred consent has been used in neonatal and paediatric research studies in several countries including the United Kingdom (Gilbert et al., 2016; Lyttle et al., 2017), Australia and New Zealand (Franklin et al., 2015; Dalziel et al., 2017; Songstad et al., 2017). It has enabled the investigation of emergency interventions that would otherwise have no evidence base. Some authors use different terms such as ‘retrospective consent’ (Songstad et al., 2017) or ‘research without prior consent’ (Woolfall et al., 2015; Woolfall et al., 2016). ‘Research without prior consent’ has been proposed because it takes account of the fact that the parents do not give consent to the initial trial procedures but only to continuation in the trial (Woolfall et al., 2016). However, in this thesis the term ‘deferred consent’ will be used in order to maintain consistency with The VoluVent Trial protocol (version 9, 21st August 2014).

6.4 Making a change to the method of consent during The VoluVent Trial

In order to improve the consent procedure used in The VoluVent Trial, the use of deferred consent was considered. This was discussed with parents who had previously declined or agreed to research studies in the unit. They indicated that deferred consent would be acceptable to them.

On 18th November 2013 the North East-York ethics committee gave a favourable opinion for a substantial protocol amendment for this trial to allow the use of deferred consent. The South Tees Hospitals NHS Foundation Trust

Research and Development department also approved the amendment. As a result, more parents gave consent for their infants to participate in the trial. The recruitment rate improved immediately, with an average of four infants per month recruited since the change of protocol.

6.5 The impact of deferred consent on the consent procedure

The use of deferred consent in The VoluVent Trial changed the consent procedure in several ways. Giving deferred consent meant that parents agreed to their infants' ongoing participation in the trial. It also meant that they agreed to the collection and use of data from their infants' medical records for the purpose of the trial. Declining deferred consent meant that such data would not be collected and that infants would no longer be managed according to the trial protocol. As the research and clinical teams were in equipoise about the two modes of ventilation, the infants of parents who declined deferred consent remained on their allocated mode of ventilation unless their clinical conditions dictated otherwise.

This meant that, regardless of their parents' decisions, the management of these infants did not change substantially. This appeared to be acceptable to parents. Many expressed relief that their decision either to give or decline consent would not lead to a change in their infants' modes of ventilation. Several stated that, because the mode of ventilation would not change and because the main purpose of giving consent was to give permission for data collection, they were willing to give consent.

However, deferred consent did affect parents' autonomy. Randomisation and initial management according to protocol had already occurred before parents were able to make a decision about the trial. This is an important disadvantage of deferred consent and is discussed further in Section 6.7.

6.6 The impact of deferred consent on this trial

The use of deferred consent had several advantages during this trial. These are consistent with published literature (Manning, 2000; Woolfall et al., 2014; Furyk et al, 2017; Songstad et al., 2017).

- Parents had more time in which to consider the trial information before making a decision.

- Mothers who had received sedatives or anaesthesia were offered information only once the effects of medication had worn off.
- In most cases, there was time for the parents of outborn infants to consider the trial information after they had arrived at the hospital. Therefore more outborn infants could be enrolled, making the results more generalisable and reducing selection bias.
- The parents' decisions to give or decline consent did not lead to a change in their infants' ventilation. This addressed a specific concern raised by parents when prospective consent was sought.
- Clinicians or researchers seeking consent were usually able to offer information at a time that better suited the parents which removed some of their reservations about approaching parents.
- The randomised mode of ventilation could be initiated immediately. This improved the scientific validity of the trial by reducing the number of infants who received a different mode of ventilation prior to randomisation.
- The recruitment rate improved after the introduction of deferred consent. The trial was therefore completed to time and target, fulfilling the research team's ethical obligation to complete the study.

6.7 Ethical considerations when using deferred consent

Deferred consent enables researchers to study interventions in emergency settings that otherwise could not be investigated. This is important in neonatal and paediatric research. It is vital that emergency interventions are based on evidence from well-conducted research rather than anecdote. Recent updates in international neonatal resuscitation guidelines (Wyllie et al., 2015) are based on evidence from trials using deferred consent or waivers of consent.

However, there are ethical aspects that must be considered before using deferred consent for emergency interventions research. These should be deliberated carefully to determine whether deferred consent is appropriate for the participants and families, the research question and the trial design. The criteria specified in the Clinical Trials Regulations (The Medicines for Human Use (Clinical Trials) and Blood Safety and Quality (Amendment) Regulations, 2008) must be adhered to.

6.8 Autonomy

Of the four ethical principles, autonomy is the principle challenged by deferred consent. Personal autonomy is the ability to self-govern (Beauchamp et al., 2001) in the context of being “free from both controlling interference by others and from limitations, such as inadequate understanding, that prevent meaningful choice” (Beauchamp et al., 2001, p.58). Therefore, informed consent is closely linked to autonomy. Clinicians and researchers have an obligation to respect a patient’s autonomy and a patient has a right to make an autonomous choice about research.

Those who argue that prospective consent for research should always be obtained highlight that deferred consent overrides the participants’ (or parents’) autonomy (Manning, 2000). They have autonomy to decide on ongoing participation but were not given autonomy to decide about initial randomisation and protocol implementation.

However, individual patients’ interests must be balanced with the responsibility to society to produce a rigorous evidence base for emergency interventions. This is vital in neonatal medicine in which many treatments are used without license or without a strong evidence base. Deferred consent allows emergency interventions to be researched appropriately and adequately. Therefore, it can be argued that it would be unethical towards the wider society not to use deferred consent as part of good trial design (Jansen-van der Weide et al., 2015; Rebers et al., 2016). Currently many unproven emergency treatments are given as part of ‘standard’ practice without consent ever being sought (Stephenson, 2006). If this is considered acceptable then implementing emergency interventions as part of an approved trial protocol that includes deferred consent should also be acceptable.

The ethical arguments either way are valid and reasonable. In the era of evidence-based medicine it would seem appropriate to use deferred consent within the regulations in order to determine the evidence. However, it is vital that the evidence for the use of deferred consent is also determined so that it can be used most appropriately and efficiently.

6.9 Current evidence regarding the use of deferred consent in neonatal and paediatric research

Deferred consent has been used in trials involving adult patients for some time (CRASH-2 trial collaborators, 2010; Perkins et al., 2016). However, it has only recently been used in paediatric trials in the UK (Gilbert et al., 2016; Lyttle et al., 2017).

Parental opinions and experiences of giving consent for research involving their children have previously been explored (Mason et al., 2000; Allmark et al., 2005; Culbert et al., 2005). In recent years, the use of deferred consent in paediatric populations has been specifically investigated (Woolfall et al., 2014; Furyk et al., 2017). The views of parents, clinicians and researchers have been obtained through qualitative research (Woolfall et al., 2013; Woolfall et al., 2014). These studies have sought qualitative data on hypothetical scenarios, retrospective data on actual trials, and nested studies undertaken prior to or during RCTs. Some researchers have assessed the impact of deferred consent on the validity of trials by reporting its effect on recruitment and the children that were included or excluded as a result of deferred consent (Harron et al., 2015; Songstad et al., 2017).

The CATCH trial (Gilbert et al. 2016) was undertaken in paediatric intensive care centres in the UK to investigate three different types of central venous catheter in children. It involved the use of prospective consent and deferred consent, and was one of the first UK trials to use deferred consent in a paediatric population. Prospective consent was used when children required central venous catheters for elective procedures. Deferred consent was used when the catheters were required as emergency interventions. The recruitment rate was higher when deferred consent was used than when prospective consent was used. A substantial proportion of parents declined prospective consent due to parental distress or preference for standard treatment (Harron et al., 2015). The authors highlighted the fact that most of the children who died in PICU could not be recruited. This was because parents declined consent, were not approached because researchers felt it was inappropriate to do so, or did not respond to approach by researchers after the death of their children. As

understandable as these reasons are, the authors highlight the inability to recruit these children limited the validity of the trial results.

The way in which deferred consent alters trial methodology and procedures can affect prognostic factors and trial outcomes. The introduction of deferred consent altered the intention-to-treat analysis in The VoluVent Trial. Initially, when prospective consent was used, analysis of data from all randomised infants was planned. When deferred consent was used, data from some randomised infants could not be analysed as consent was not obtained for all of them. This may have affected the balance of prognostic factors between the two groups which could then have affected the results. This is discussed further in Section 7.5.5 of Chapter 7 Discussion.

Songstad et al. (Songstad et al., 2017) reported the impact of deferred consent on a neonatal emergency interventions RCT comparing two types of NIV in preterm infants. They found that deferred consent led to higher recruitment rates. Interestingly, in their study, making a change from prospective to deferred consent was associated with a change in maternal and infant demographics. After the introduction of deferred consent, fewer mothers of enrolled infants had been exposed to antenatal steroids and more had received intrapartum antibiotics. The authors postulate that this may be because deferred consent enabled the enrolment of more infants from unexpected deliveries. This requires further evaluation and is an example of the impact of deferred consent on trial population demographics.

The CRASH-2 trial collaborators (CRASH 2 trial collaborators, 2010) reported on an RCT investigating the use of tranexamic acid in adult trauma patients. This large multi-centre trial used a variety of different consent procedures at different sites, including deferred, waived and proxy consent. A logistic regression analysis was performed exploring 'time to treatment' as an explanatory variable on the outcome of mortality due to bleeding. They estimated that a delay of one hour in administering the trial treatment reduced the proportion of people who benefitted from the treatment from 63% to 49% (Roberts et al., 2011). The authors argue that, in emergency interventions research, a delay in starting a trial treatment due to the need to obtain prospective consent may increase mortality in the trial population. Secondly, a

delay may also conceal the true treatment effect that may then affect translation of a trial's findings into clinical care. The delay caused by the need to seek consent may dilute the effect of an emergency intervention on the trial population. A stronger or positive effect may be seen in clinical practice during which the same emergency intervention would be given immediately without seeking consent.

6.9.1 Parents' experiences of deferred consent

Parents have indicated that deferred consent is acceptable to them when used in trials comparing standard treatments (Woolfall et al., 2014). There is less evidence to suggest that they consider it to be acceptable when a novel treatment or placebo is being used. However, two trials are currently underway in the UK and Australia comparing the use of a standard drug for the emergency treatment of childhood status epilepticus (phenytoin) with a non-standard drug (levetiracetam) (Dalziel et al., 2017; Lyttle et al., 2017;). The EcLiPSE trial is being undertaken in the UK (Lyttle et al., 2017). This is the first time deferred consent has been used in a paediatric emergency interventions trial involving a non-standard intervention. Prior to commencing the EcLiPSE trial, qualitative research was undertaken exploring parents' views on the use of deferred consent in such a trial. Parents were initially uncomfortable with the prospect of deferred consent. However when parents were informed of the rationale for the trial, including the fact that the standard treatment has important side effects, the majority indicated that the use of deferred consent would be acceptable (Woolfall et al., 2014). These data informed the design of the EcLiPSE trial that now includes a nested study investigating the experiences of parents approached for consent for this trial (Lyttle et al., 2017).

A similar qualitative study was undertaken prior to the Australian trial comparing phenytoin and levetiracetam for the treatment of childhood status epilepticus (Dalziel et al., 2017). This study was slightly different in that the parents interviewed had experience of children receiving emergency care for minor illnesses in the Emergency Department rather than more serious conditions such as status epilepticus. As a result, they were asked about hypothetical scenarios regarding children needing higher levels of care than their children has received. Parents in this study had mixed views on the use of deferred

consent. The majority did find it acceptable provided that the interventions were both used as standard care. In keeping with the findings by Woolfall et al. (Woolfall et al., 2014) parents were less comfortable with the idea of deferred consent for a trial of a novel or high-risk intervention.

Similar data were obtained by O'Hara et al. (O'Hara et al., 2018). They explored the views of bereaved and non-bereaved parents on 'research without prior consent'. This was part of a feasibility study to inform a pilot emergency interventions trial on the use of fluid boluses for children with septic shock. Twenty-one parents were interviewed for this trial, including seven bereaved parents, and all had had children who had recently been admitted to UK hospitals with severe infection. After they had discussed the need to establish an evidence base for the use of fluid boluses and the need to administer the interventions without delay in an emergency, all 21 parents stated that they would have given consent for such a trial.

Much of the qualitative research done on parental views of the use of deferred consent in the paediatric population has focused on children and young people, with less emphasis on the neonatal population. Therefore this is an area that requires further explanation. Seeking consent for neonatal trials is unique. Proxy consent is always required. Parents of newborn infants are in a uniquely vulnerable position. The mother may be physically and mentally vulnerable due to the effects of labour and interventions at delivery. The father may be anxious about the condition of the mother as well as the infant. Both parents may be fatigued and emotionally vulnerable. Many parents are unmarried, meaning that, in the first few days of life, only the mother has parental responsibility. In addition to all of these factors, parents have to make a decision based on what they think is best for an infant that they have potentially only just met.

The use of deferred consent in The VoluVent Trial appeared to be acceptable to the majority of parents and this is manifest by the fact that most parents gave consent for the trial and did not raise objections to the fact that their infant had already been managed according to a trial protocol. However, it would be dangerous to assume that it was acceptable to all parents and that they did not have any objections. At the time that consent was sought they may not have been able to raise objections, either because any objections that they had arose

at a later date or because their concerns about other aspects of the infant's condition took precedence over any concerns about research. They may also have felt unable to raise concerns about the consent process because of fear about the effect on their relationship with their child's clinical team. These are possibilities but parental experiences of deferred consent in this trial need to be investigated before a larger trial can be undertaken.

6.9.2 Clinicians' and researchers' experiences of deferred consent

Published literature on the use of deferred consent reveals themes that relate to the experiences of clinicians and researchers in its use in paediatric and neonatal settings. The majority of those who had not used deferred consent for paediatric research thought that it would have a negative impact on the parent-practitioner relationship whereas the majority of those who had used it before thought that it had no impact on the relationship (Woolfall et al., 2013).

Foglia et al. (Foglia et al., 2017) studied a different group of researchers but also identified differing responses depending on prior experience of deferred consent. They surveyed participants at the Fourth International Neonatal Resuscitation Research Workshop in 2015. Their sample of 47 respondents consisted of neonatal researchers, some of whom were on national and international neonatal resuscitation committees. The survey questions related to research in the delivery room immediately after the birth of an infant. Half of the participants had prior experience of using deferred consent and half did not. The levels of comfort regarding deferred consent for minimal risk or comparative effectiveness delivery room studies were similar between groups. However, prior experience of using deferred consent was associated with a greater proportion of respondents feeling comfortable with using it to investigate novel treatments in the delivery room. Only 33% of those with prior experience of deferred consent stated that it is possible to produce scientifically valid delivery room research using antenatal prospective consent, compared with 50% of those without experience of it. Compared to the study by Woolfall et al. (Woolfall et al., 2013), the respondents were concerned about the methodological limitations in using prospective antenatal consent. Given the target population of this survey, that is to be expected.

Clinicians and researchers working in the neonatal unit at The James Cook University Hospital had little or no experience of using deferred consent prior to its introduction during this trial. The ethical reasons for changing the consent method were discussed with all those authorised to take consent before the protocol amendment was made. Extra training sessions were undertaken and written guidance produced so that those seeking deferred consent were aware of the practical and theoretical differences of using this method compared to prospective consent.

When deferred consent had been used for almost two years as part of this trial, a formal meeting was held to discuss approaches to consent for all of the neonatal research studies that were active in the unit at that time. The research team, the unit's Consultant Neonatologists and senior nurses attended the meeting. By then it was clear that the use of deferred consent had led to a process of "experiential learning" (Woolfall et al., 2013) through which clinicians and researchers seeking consent had learnt how to better judge the time at which to approach parents. The team had developed a collaborative approach to seeking consent, following patterns of approach agreed by all team members but tailored to each individual infant. These patterns of approach facilitated the consent process for each study and therefore facilitated co-enrolment into multiple studies.

The experience of the Principal Investigator for The VoluVent Trial was that, when compared with prospective consent, deferred consent requires a more detailed discussion with parents. In response to parents' questions, and in order to be open and transparent, this discussion usually included the topics of consent methodology and the ethical issues in seeking consent for research studies. In the neonatal intensive care setting, in the hours after a preterm infant eligible for an emergency interventions trial has been born, deferred consent allows the parents more time to consider information. It also enables the research team to approach them at a time that is appropriate for the parents.

Deferred consent appears to have been acceptable to all of those authorised to seek consent for this trial but their views and experiences have not been studied. If a similar ventilation trial were to be undertaken on a larger scale, this is an important area of qualitative research that would need to be embedded

into the design of that larger trial. This would ensure that the appropriate regulations, guidance and training could be provided to the clinicians and researchers who would be required to seek consent. This would aim to ensure similar standards and quality of practice if deferred consent were to be sought in multiple centres.

6.10 Deferred consent in the context of a complex interventions trial

The VoluVent Trial demonstrated that seeking prospective consent from parents of newly born preterm infants for enrolment into a complex interventions trial was neither appropriate nor practical. The use of deferred consent

- appeared to be more acceptable to both parents and to those seeking consent,
- improved the scientific validity and generalisability of the results and
- improved the recruitment rate.

The use of deferred consent in this trial appeared to be acceptable to the majority of parents but, as discussed above, this observation needs to be formally investigated. Investigating parental views on its use in a complex interventions trial could also be considered. As discussed earlier, changing consent method from prospective to deferred consent changed one of the reasons for asking parental consent. They were not being asked to decide whether their infant should be randomised and a trial intervention initiated. They were being asked to give permission for the trial protocol to continue and for the collection of data. Did this change the amount of information that the parents wanted regarding the complexity of the interventions in order to make an informed decision? If so, did they need more or less information to make a decision and would the decision have been easier or harder if prospective consent had been used? Did it, as Manning suggests (Manning, 2000), actually alleviate them of the burden of having to consider complex information in the first few hours after the birth of their premature infants? It is possible that the use of deferred consent in this particular complex interventions trial may have made the decision-making process easier for parents. However, although clinicians and researchers have raised these possibilities (Manning, 2000), only parents can provide the answers and researchers should not presume that they know the answers to these questions.

The need to change the method of consent during this trial highlighted the importance of using qualitative research to choose the most appropriate method of consent during the design stage of a study. Whilst designing this trial, advice was sought from parents about the content of the participant information sheet but their input on the most appropriate method of consent was not sought. When designing this trial on a larger, multi-centre scale it would be necessary to embed a nested qualitative study to investigate parents' experiences of consent for neonatal emergency interventions research.

6.11 Future directions

The use of deferred consent is now being used more widely and facilitates research into emergency interventions. When used judiciously by researchers experienced in seeking deferred consent, well versed in its ethical benefits and challenges, and knowledgeable of the scientific basis of a particular trial, deferred consent appears to be acceptable to most parents and clinicians. There are still gaps in knowledge about its use, particularly as to the best method of seeking deferred consent from parents whose child has died (Woolfall et al., 2015).

Therefore further qualitative research is needed into the use of deferred consent in neonatal research studies. Areas that should be considered include whether parents feel relieved about not having to decide on initiation of a trial protocol and whether they would feel the same about a study comparing two 'standard treatments' and a study investigating a novel treatment.

Chapter 7 Discussion

7.1 Introduction

This is the first randomised controlled trial to compare two types of VTV in preterm infants. The results provide new data with which to plan a larger study. This pilot trial also provides important information on how to approach challenges in designing and implementing a trial of complex interventions in a neonatal intensive care setting. This information will be crucial to the design of a larger trial comparing VTV modes in preterm infants and is also applicable to the design of other neonatal emergency interventions trials.

This chapter discusses some of the important outcomes from this trial, how they can be used to develop a larger trial, and the strengths and limitations of the trial.

7.2 Effect of two VTV modes on readiness for extubation in preterm infants

The trial results demonstrated a clinically relevant difference between VCV and VG in the primary outcome. In the VG group the median duration of time taken for an infant to be ready for extubation was 23 hours (95% CI 10.8 – 35.2 hours). In the VCV group the median duration was 36 hours (95% CI 18 – 54 hours).

A difference of 13 hours of ventilation represents a potentially important difference in ventilation-associated lung injury (VALI) between the two groups. The results suggest that it is possible that VG has the potential to reduce exposure to volutrauma. However, this single centre trial was not designed to confirm lung injury although this is an appropriate outcome measure for neonatal trials. Indirect measures of VALI, such as a clinical diagnosis of chronic lung disease, could be used in a future trial but would require a much larger sample size and detailed statistical techniques to adjust for covariates. A difference of 13 hours may also have a health economic benefit.

More than half (62%) of the trial population had reached the 'success' criteria by 48 hours. Three quarters (76%) had reached the 'success' criteria by 96 hours. The majority of infants requiring ventilation beyond this time point were the extremely preterm infants (<28 weeks' gestation). This is not surprising given

their greater immaturity. However it demonstrates another important research question as to whether one mode of VTV is more beneficial than another for different gestational age groups.

7.3 Effect of two VTV modes of different gestational age groups

Regardless of the mode of ventilation used, infants in this trial reached the 'success' criteria much quicker in the 28 – 33+6 weeks' gestation group compared with the <28 weeks' gestation group (median time 20 hours, 95% CI 16.7 – 23.3 hours, and 93 hours, 95% CI 9.8 – 176.3 hours respectively). The unadjusted HR was 3.32 (95% CI 2.1 – 5.3). This strongly indicates a three-fold increase in the risk of meeting the 'success' criteria at any time point in the 28 – 33+6 weeks' gestation group. This is not surprising given that more mature preterm infants usually require shorter periods of ventilation than extremely preterm infants. It justifies the use of stratification according to these gestational age groups when designing this trial and is an important strength of the trial.

The pre-specified sub-group analyses were planned as exploratory analyses and were not powered to show significant differences between groups. However, the results demonstrate potentially important differences between VCV and VG in the sub-groups. These differences could be evaluated further in a larger trial powered to show any differences in treatment effect across sub-groups.

7.3.1 Effect of VCV and VG in infants born at <28 weeks' gestation

In the extremely preterm infants (those born at <28 weeks' gestation), the median time to 'success' criteria was shorter in the VCV group (79 hours, 95% CI 0 – 177.7 hours) compared with the VG group (102 hours, 95% CI 90 – 204.7 hours). This is an average difference of 23 hours between groups. The wide CIs associated with these results reflect the high degree of uncertainty about these results. However, 23 hours is a clinically relevant difference and worth investigating with a larger trial. Although almost two thirds (59%) of infants in this group had reached the 'success' criteria by 96 hours this group also accounted for most of the infants who required ventilation for longer than this.

7.3.2 Effect of VCV and VG in infants born at 28 – 33+6 weeks' gestation

In the 28 – 33+6 weeks' gestation group, there was a shorter median time to 'success' criteria in the VG group (19 hours, 95% CI 16.5 – 21.5 hours) compared with the VCV group (24 hours, 95% CI 11.9 – 36.1 hours). The difference between groups here was an average of only five hours. This is not a strikingly relevant difference clinically but, as stated previously, the histological effects are unknown and it is possible that five more hours of ventilation in the VCV group may contribute to greater VALI in that group. The results of this trial cannot address this.

7.3.3 Frequency of pneumothorax

The overall incidence of pneumothorax occurring whilst on the trial mode was low (7%). However, there was an imbalance between the two groups. Only one infant in the VG group developed a pneumothorax whilst receiving VG, compared with seven in the VCV group. The numbers of infants are too small to draw any conclusions about this. However, pneumothorax is an important short-term complication of mechanical ventilation and can have serious sequelae (Jarreau, 2015a). It represents macroscopic evidence of VALI. Therefore, in this regard, these results provide important information regarding choice of secondary outcomes measures in a larger trial. With a larger sample size, regression analyses could determine whether the mode of VTV independently increases the risk of developing a pneumothorax.

7.4 Strengths of the study

7.4.1 Study design: comparison of two modes of VTV

This randomised controlled trial is the first study to compare two types of VTV in newborn infants using clinically relevant outcomes. It was undertaken following the Cochrane review comparing PLV with VTV published in 2010 (Wheeler et al., 2010). The authors recommended that further research should include comparisons of different volume-targeting modes and strategies. The updated Cochrane review in 2017 (Klingenberg et al., 2017), which included analyses of more recent research studies, still contains the same recommendation that volume-targeting strategies be researched. Therefore this trial contributes unique data to the field of research of using VTV in newborn infants.

7.4.2 Study design: methodology

The VoluVent Trial is an example of a trial of complex interventions (Craig et al., 2008). These interventions (modes of ventilation) were studied in a complex environment (an intensive care unit) involving complex patients (preterm infants) and complex operators (neonatal nurses and doctors). Therefore it was necessary to design a protocol that was rigorous enough to produce scientifically valid results but flexible enough to be successfully implemented and completed in a busy neonatal intensive care unit (NICU).

The points below describe some of the ways in which this was achieved.

7.4.2.1 Designing the trial

When designing the trial the protocol was drafted by the Principal Investigator with oversight from senior Co-Investigators. It was then discussed with all Consultant Neonatologists and with senior nurses in the unit. Their feedback on certain practical aspects of the protocol contributed to re-drafted and updated versions. It was then produced as the final document and was then submitted to the ethics committee and regulatory body for approvals.

This engagement with the clinical team ensured that the protocol was acceptable to, and supported by, senior team members. The protocol was implemented thoroughly and achieved good fidelity (Craig et al., 2008). The trial recruited to time and target. These aspects demonstrate that the trial, whilst using standardised outcome measures and follow up, was feasible and practical.

7.4.2.2 Implementation of training packages

Volume guarantee had not been used in routine practice in the unit prior to the design of the trial. Five months before recruitment started the Principal Investigator implemented a training package for all team members caring for ventilated infants in the unit. The training consisted of seminars, practical workshops and bedside teaching on the use of VG, VCV and the trial protocol. Ad hoc training sessions were also provided. The Principal Investigator also delivered these training sessions to all new starters within the team, including new groups of junior doctors, on a routine and ad hoc basis. The Principal Investigator was employed as the unit's Clinical Research Fellow in

Neonatology and always contactable in person or by telephone to provide additional guidance throughout the course of the trial. These measures aimed to ensure that there was good fidelity with the trial protocol (Hasson, 2015).

7.4.2.3 Randomisation

Preparation of the randomisation sequences was undertaken by the Deputy Director of the Clinical Effectiveness Unit at South Tees Hospitals NHS Foundation Trust. He remained independent of the trial throughout and was the only person who knew the randomisation sequence. Block randomisation was computer-generated. Two separate block randomisation sequences were prepared, one for each stratification group. The randomised allocations were sealed within sequentially numbered opaque envelopes. This is a standard randomisation procedure recommended by the MHRA (Medicines and Healthcare products Regulatory Agency, 2012). The research and clinical teams had no knowledge of, or access to, the randomisation sequences during the trial. A record of these sequences was kept by the Deputy Director of the Clinical Trials Unit until the trial had finished.

The research team, clinical team and parents did not know which mode of ventilation an infant would receive until the infant had been randomised. Once the envelope had been opened they could not be blinded to the allocation because this is not currently possible in a ventilation trial. After randomisation, the envelopes and the allocations within them were kept by the Principal Investigator in a locked cabinet. This complies with good practice as outlined by the Medicines and Healthcare products Regulatory Agency (Medicines and Healthcare products Regulatory Agency, 2012).

Compliance with MHRA guidance about randomisation is another area of strength in this trial. It prevented selection bias and achieved a good balance across treatment groups and with prognostic factors.

The CONSORT diagram (Figure 4-1) shows that 73 infants were randomised to receive VCV and 69 infants were randomised to receive VG. This reduced allocation bias because the randomisation procedure ensured almost equal allocation of infants between the two arms of the trial. In addition equal numbers of infants in either arm of the trial were excluded after randomisation because deferred consent was not obtained. This reflects the absence of sampling bias

and the maintenance of equipoise by the research and clinical teams throughout the trial. Finally, the results tables in Table 4-4 and Table 4-5 show that there were similar numbers of infants randomised to either mode of ventilation in both of the stratification groups. Again, this reflects that randomisation minimised bias by achieving an excellent balance of the two modes of ventilation within the trial population.

7.4.2.4 The primary outcome measure

Definition: The primary outcome measure was the duration of time, in hours, from starting the allocated mode of ventilation until reaching the pre-defined 'success criteria'. These criteria consisted of maintenance of a MAP <8 cmH₂O and FiO₂ of ≤0.35 for six consecutive hours, followed by a successful SBT (Kamlin et al., 2006). Use of these criteria ensured that the primary outcome was objective and standardised for all infants in the trial. These pre-defined 'success criteria' were chosen to reflect 'readiness for extubation'. Use of these criteria removed the subjective bias that would have occurred if the outcome had been dependent on clinicians' opinions regarding readiness for extubation.

Clinical relevance: The primary outcome measure was chosen to reflect the duration of time taken from starting the allocated mode of ventilation to being 'ready for extubation'. This outcome measure is relevant when using VTV in newborn infants. Ventilator-associated lung injury (VALI) is a side effect of ventilation (Jobe et al., 1998). The earlier an infant is ready for extubation, the shorter the duration of exposure to mechanical ventilation and to volutrauma. This outcome measure is of clinical importance in the management of infants at risk of VALI. Therefore, for this single centre trial, the chosen primary outcome measure was relevant for a comparison of ventilator modes aimed at controlling tidal volumes.

Pragmatic actions: Some infants were extubated without having met the 'success criteria'.

Six infants had unplanned extubations but had good respiratory drive and were not re-intubated. This had been pre-determined in the trial protocol because it would not have been appropriate to re-intubate these infants just for the purpose of the trial. In practice these infants were recorded as having met the primary outcome if they remained extubated for at least 24 hours.

Ten infants had a planned extubation before reaching the 'success criteria'. These infants fell into two groups. The first group consisted of three infants who became hypocarbic despite maximal weaning of ventilation but who continued to have a MAP of at least 8cmH₂O. As hypocarbia is a risk factor for brain injury in infants (Okumura et al., 2001; Erickson et al, 2002) the clinical team deemed it necessary to extubate these infants without delay in order to avoid ongoing hypocarbia. This was considered by the clinical and research teams to be in those infants' best interests. Therefore planned extubations due to hypocarbia were not deemed to be major protocol deviations. The infants were recorded as having had the primary outcome if they remained extubated for 24 hours.

The second group of seven infants consisted of those who had been ventilated for a prolonged period of time but appeared ready for extubation despite not having reaching the 'success' criteria. Attempted extubation was deemed necessary by the treating Consultant Neonatologist in order to avoid prolonged, unnecessary ventilation. These infants had not reached the 'success' criteria because either the MAP remained ≥ 8 cmH₂O or the FiO₂ remained >0.35 , or both. These planned extubations were not deemed to be major protocol deviations. The infants were recorded as having had the primary outcome if they remained extubated for at least 24 hours.

These sixteen infants did not reach the defined 'success' criteria. However the decisions to extubate them were acceptable and pragmatic within this particular trial. These actions revealed necessary adjustments that would need to be applied to a protocol for a larger trial (Richards, 2015)

Cost implications: Although a health economic evaluation was not planned, the primary outcome measure also has possible cost implications. A ventilated infant is defined as an infant requiring intensive care (Craig et al., 2011). In the UK the definition of one intensive care day is "any day where a baby receives any form of mechanical respiratory support via a tracheal tube" (Craig et al., 2011). It is important to investigate whether one particular mode of VTV enables infants to be ready for extubation sooner than another mode. Being ready for extubation sooner implies the need for a shorter duration of mechanical ventilation. This may then translate into a possible reduction in the cost of providing intensive care for ventilated infants.

In this trial, the median time to 'success' criteria in infants in the VG group was 23 hours (median time to 'success criteria', 95% CI 10.78 – 35.22 hours). In those who received VCV the median time was 36 hours (95% CI 18.03 – 53.97 hours). The limitations of the trial's sample size are discussed in Section 7.5.1. However if this difference were seen in a larger trial, it would indicate a potential cost benefit in using VG in that the cost of intensive care provision would be reduced from 2-3 to 1-2 days.

However, health economic evaluations are more complex than this. For example, it is also possible that earlier extubation may lead to higher rates of re-intubation. Rates of re-intubation were reported as part of this trial and no difference was seen between the two groups. However this was a secondary outcome measure for which the trial was not powered. A longer-term health economic analysis planned as part of a larger trial would provide important information on the cost of these modes in the context of this secondary outcome.

7.4.2.5 Evaluation of the primary outcome measure

An ancillary study was undertaken to assess the validity of one of the chosen 'success criteria' forming part of the primary outcome measure. The strengths and limitations of that ancillary study have been discussed in detail in Chapter Five. This ancillary study contributed substantially to the strengths of The VoluVent Trial because it tested the validity of the primary outcome measure. There are no other published studies comparing manually recorded MAP values with those recorded electronically at much higher sampling rates. Therefore the ancillary study provides unique data as well as validating the trial's primary outcome measure.

The ancillary study showed that the MAP values documented once every hour by a nurse closely reflect the values recorded electronically with every breath during that same minute. These were also validated by measurements being sampled at 100Hz. This strengthens the validity of the primary outcome measure. It demonstrates that one MAP value documented manually by a nurse once an hour is representative of the MAP values being generated continuously during VG and VCV ventilation.

The ancillary study also provides data that are useful for routine clinical practice. The use of electronically recorded data as part of routine practice is gaining popularity in UK NICUs. However manually recorded physiological and ventilatory data still form part of standard practice in many units. The results of this ancillary study show that manually recorded MAP values show a high level of agreement with those sampled more frequently using computer software. Therefore, these data show that manual recording of MAP measurements is valid and reliable.

7.4.3 Inclusion of a statistical analysis plan

A major strength of this study was the use of a pre-determined SAP. There is increasing recognition of the importance of SAPs (Chen, 2013) by funders, regulators and journals. In accordance with Good Clinical Practice guidance (Medicines and Healthcare products Regulatory Agency, 2012) a SAP was compiled for this trial by the Principal Investigator. During its compilation the SAP underwent several version-controlled revisions under the supervision of a senior statistician from Newcastle University's Institute of Health and Society's Biostatistics Group.

The sixth version of the SAP was used by another statistician from the Institute of Health and Society's Biostatistics Group at Newcastle University. This statistician used it to undertake an independent, blinded analysis of interim data from 50 infants as part of the trial oversight review. This demonstrated that the SAP was clear and comprehensive enough that independent analyses of data on demographics, characteristics and the primary outcome could be performed.

The blinded analyses were used by an independent clinical reviewer to create the trial oversight report. The SAP was updated on the basis of that report. The Principal Investigator remained blinded to that interim analysis until full recruitment had completed. The Principal Investigator undertook analysis of the full dataset only after the final version of the SAP (version 11, dated 8th July 2016) had been completed.

The use of a SAP, and adherence with the procedures described above, demonstrate a thorough and transparent approach to statistical planning and data analysis (Gamble et al., 2017). The SAP ensured that the trial's statistical approach could be updated on the recommendation of the trial oversight

reviewer. This was done to ensure that the statistical approach reflected the distribution of the primary outcome data. This 2-stage analysis has been identified as good practice in recent published guidance on SAPs (Gamble et al., 2017). It did not require a protocol amendment because the original statistical approach was undertaken. However, it did allow the data to be presented in a descriptive manner that was appropriate for the sample size. It also allowed incorporation of early phase trials methodology (Jung, 2008) into the statistical approach which was relevant for a pilot trial.

This approach, as described in the final version of the SAP, enabled effective use of the results and data generated by this pilot trial. Use of HRs and CIs for the time-to-event analyses encouraged a greater emphasis on the descriptions of the data, and their merits and uncertainties (Kyriacou, 2016). Incorporation of the early phase trials methodological approach enabled the identification of a 'response threshold' that could allow the development of a larger trial. The SAP enabled an exploratory approach that would inform the design and statistical approach of a larger trial. Analysis and presentation of data in this way is appropriate for pilot trials (Lancaster et al., 2004; Lee et al., 2014).

The use of a detailed SAP for this trial also ensured that the validity of its results can be tested in future by independent researchers. The statistical methods can be checked thoroughly by clinicians, researchers, peer-reviewers, editors, and parent or patient groups. This allows transparency regarding the data derivation, statistical methods and interpretation of the results. It will also improve the ability of those interested parties to determine whether the results are applicable to them.

7.4.4 Statistical approach using early phase trials methodology

The use of early phase trials methodology described by Jung (Jung, 2008) was appropriate for this pilot trial. No difference was seen between the two groups in the event rates (number of infants reaching the 'success' criteria) at 48 hours. This may be because the choice of 48 hours as a time point was made using data from a previous trial (Singh et al., 2006). The plan to use this time point was based on the proportion of events seen in the previous trial by Singh et al (Singh et al., 2006). They compared VCV with PLV and showed a substantial difference in events at 48 hours.

However, such a difference was not apparent in The VoluVent Trial. This may have been because VG and VCV are both modes of VTV and therefore it is more difficult to show such a striking difference. Figure 4-4 shows the time-to-event analysis for the first 240 hours of The VoluVent Trial. Table 4-13 shows the event rates for both groups at every 24 hour time period for the first 96 hours after enrolment. A greater difference was seen between the two groups at 24 hours after enrolment. This indicates that the first 24 hours of ventilation may be a more appropriate focus for this primary outcome in a larger trial.

7.4.5 Use of deferred consent

The use of deferred consent is a major strength of this trial. After a protocol amendment it led to a marked improvement in recruitment. In doing so, it ensured that recruitment was completed to time and target. It also appeared to be more acceptable to parents. Some parents volunteered opinions that they were comfortable with the fact that deferred consent did not lead to a change in their infant's treatment. Deferred consent also ensured that infants could receive their allocated mode of ventilation as soon as possible. This improved the ethical and scientific validity of the trial and also allowed parents more time in which to make a decision about participation.

The amendment in consent method and subsequent improvement in recruitment demonstrate the value of a pilot trial in identifying and addressing challenges in undertaking complex interventions research (Ukoumunne et al., 2015). A previous trial led by the same unit compared two modes of mechanical ventilation and recruited 109 infants over a period of 29 months (Singh et al., 2006). That trial involved two participating centres. Ninety infants in that trial were recruited at the same centre as The VoluVent Trial. The authors of the previous trial did not report difficulties in recruitment using prospective parental consent obtained within six hours of starting mechanical ventilation. Two decades later, it is not clear why it was more difficult to obtain prospective consent for The VoluVent Trial. Recent research has reported qualitative data on parental experiences of different consent methods in paediatric emergency care trials (Harron et al., 2015). However there is still a gap in knowledge regarding parents' experiences of different consent methods in the neonatal intensive care setting.

The VoluVent Trial has therefore highlighted an area for further qualitative research. This could involve nested qualitative research before and within a larger trial comparing modes of VTV.

7.4.6 Co-enrolment

This trial site has been a research-active unit for many years. Like many such units, co-enrolment of infants into more than one research study is supported at the trial site provided that the burden on parents is minimised and contamination of simultaneous protocols does not occur. Many infants in this trial were eligible for other concurrent trials ongoing in the unit at the same time. Some were co-enrolled into these trials after enrolment into The VoluVent Trial.

Published literature suggests that most parents are willing to allow their infants to be enrolled into more than one study. Morley et al. (Morley et al., 2005) asked 98 parents in a large tertiary NICU for their opinions regarding co-enrolment. These parents had previously been asked to join at least two studies although not all had agreed to do so. Seventy six per cent of respondents stated that they would be prepared to allow their infant to be enrolled into more than one study. Harron et al. (Harron et al., 2012) described the co-enrolment process in two trials involving emergency and elective interventions in two paediatric intensive care units (PICUs). Data from one unit were limited but data from the other showed that all but one of the children enrolled into the first trial were also enrolled into the second (with the second trial using a deferred consent process). However, there is little published qualitative data on this subject. Qualitative research investigating parents' views on co-enrolment on both a broader and a more focused scale could inform the design of future studies.

Practical and ethical issues regarding co-enrolment did arise during this trial. The strategy undertaken to address these issues are described in Section 4.2.9 of Chapter 4 Results. This strategy demonstrated a considered and ethical approach to co-enrolment. The aim was to balance the obligations of minimising the burden on parents whilst ensuring that parents had access to information about all studies and could make their own decisions about co-enrolment. The strategy also demonstrated an approach that aimed to minimise selection bias in the trial populations of the concurrent studies. Enabling co-enrolment with full

parental consent ensured that infants were not excluded from some studies just because they had been enrolled into another study previously. This increased the generalisability of the results of all of the concurrent trials.

However, despite the ethos of aiming to facilitate co-enrolment to prevent bias, the research team also had to ensure that concurrent studies did not lead to protocol contamination. Therefore two trials were not introduced at the trial site during the recruitment period for The VoluVent Trial. The protocols for these trials were discussed by the research team and were deemed to be incompatible with that of The VoluVent Trial.

One of those two trials, The HIPSTER trial, was a non-inferiority trial comparing two methods of NIV as primary respiratory support in preterm infants (Roberts et al., 2016). The target population was infants who had never received surfactant or mechanical ventilation. The VoluVent Trial protocol specified that all preterm infants should receive CPAP after birth if they required NIV. This standardised the mode of NIV for infants who may subsequently become eligible for The VoluVent Trial. The HIPSTER trial protocol (Roberts et al., 2015) would have prevented this standardisation of NIV. This could have potentially affected The VoluVent Trial's population characteristics. Use of two different modes of NIV may have lead to differences in the infants' lung disease at the time of intubation. This may have then affected The VoluVent Trial's primary outcome result.

The second trial was a randomised controlled pilot trial investigating use of a low dose corticosteroid to facilitate extubation in ventilator-dependent preterm infants (Yates et al., 2016). This double-blind placebo controlled trial would have altered the respiratory management of some infants already enrolled in The VoluVent trial. It too could have substantially affected the primary outcome result.

The challenges of co-enrolment that arose during this trial highlighted the way in which the themes of ethical obligations, patient involvement and good trial conduct can affect any aspect of any research study. They also emphasise the need to balance the obligations of clinical and research teams towards individual infants and parents with the wider obligations of ensuring that research studies can complete recruitment with generalisable patient

populations. These issues were described by Brocklehurst in 1997 (Brocklehurst, 1997) and remain relevant today.

7.4.7 Trial monitoring

As part of research governance procedures the South Tees Hospitals NHS Foundation Trust's Research and Development department undertook two monitoring visits to scrutinise the conduct of the trial. A favourable report was given on both occasions.

As advised by the sponsor, this study did not require a formal Data Monitoring and Safety Committee. However, in line with Good Clinical Practice guidance (Medicines and Healthcare products Regulatory Agency, 2012), we did request a trial oversight review of data from the first 50 infants to be enrolled (see Appendix 9.8). This review was undertaken by an independent statistician and clinical reviewer. They were blinded to the interventions allocated to infants.

These monitoring exercises were a major strength of this trial. They demonstrated awareness of, and practice consistent with, Good Clinical Practice guidance (Medicines and Healthcare products Regulatory Agency, 2012). In light of the trial oversight review report we reviewed the sample size calculation because the review had indicated that the data were unlikely to be normally distributed. A retrospective calculation using non-parametric tests showed that a larger sample size would be needed to show a statistically significant difference between the two groups with a power of 80%.

Therefore the decision was made to present the results as summary statistics rather than being hypothesis testing. The SAP was updated prior to analysing the data.

7.5 Limitations of the study

7.5.1 Sample size

The sample size for this trial had been calculated using parametric tests based on the results of a previous ventilation trial done at the same trial site (Singh et al., 2006). Parametric tests were used because the previously published primary outcome data had been presented using mean values. However, the data from The VoluVent Trial were not normally distributed. Therefore Kaplan-

Meier time-to-event analyses with Cox proportional hazards ratios were used to analyse the primary outcome data.

A retrospective sample size calculation using a non-parametric log-rank test showed that 178 infants would be needed to show a statistically significant difference between the two groups in the number of infants reaching the 'success' criteria at 48 hours with a power of 80% and a significance level of 0.05. Therefore a fully powered trial would require at least 178 infants. During The VoluVent Trial nine infants did not reach the 'success' criteria and one infant was withdrawn after consent had been obtained. These 10 infants represent 8.8% of the 113 infants originally enrolled into The VoluVent Trial. To account for a similar proportion of censored data and withdrawals in a larger trial, a further 16 infants (8.8% of 178) would be required. Therefore, a fully powered trial would require a sample size of at least 194 infants.

The sample size for The VoluVent Trial was not large enough to test statistically for treatment effect using the log-rank analyses. However, results of pilot trials are not definitive and should not be interpreted as such (Arnold et al., 2009; Lancaster et al., 2004). The results were therefore presented as summary statistics focusing on the descriptive analyses and, crucially, based on non-parametric Kaplan-Meier time-to-event analyses. They were not used to test the original hypothesis and this is appropriate for a pilot trial (Lancaster et al, 2004).

7.5.2 Single centre study

This study was undertaken in one centre. Both inborn and outborn infants were included and only nine sets of parents (who were present at the trial site) were not approached to discuss the trial. These measures aimed to ensure that the trial data were as generalisable as possible. They also ensured that as many parents as possible had the chance to consider their infants' participation in the trial.

However, by its nature as a single centre study, this trial is limited in the generalisability of its findings to other centres. Ninety one per cent of the enrolled infants had mothers whose ethnic background was White British. This is slightly higher than the 86% reported for the Middlesbrough ward (Tees Joint Strategic Needs Assessment, Middlesbrough JSNA Ethnicity). It may reflect the fact that infants from all parts of the North East and North Cumbria, as well as

other regions of the UK, were enrolled. Ethnicity is one characteristic used as a measure of generalisability. However other characteristics such as social deprivation could also be used and incorporated into the design of a larger trial.

7.5.3 Unmasked interventions

After randomisation the clinicians, researchers and parents were aware of the mode to which all infants had been allocated. It is currently not possible to mask a mode of ventilation whilst it is in use. To aim to minimise the risk of bias a detailed trial protocol was used and detailed instructions regarding the protocol and trial procedures were available at the cotside of each enrolled infants. However, despite this, the unmasked interventions may have led to both performance and detection bias (Higgins et al., 2011).

7.5.4 Concomitant medications

The use of concomitant therapies that can impact on the respiratory outcomes of infants were permitted in this trial. These included postnatal steroids (Doyle et al., 2017b), medical and surgical treatment for a PDA, inhaled nitric oxide, and sedatives (Donn et al., 2017a).

The use of sedatives was specifically monitored with respect to the timing of the SBT. However, the protocol and SAP did not mandate that the use of sedation at other times, or the use of inhaled nitric oxide, should be recorded. These therapies are used infrequently in preterm infants at the trial site and therefore are unlikely to have had a large effect on the results. There may have been an imbalance in their use between the two arms that is not recorded. This may not have affected the results in this small trial but could have caused performance bias. Data on these therapies should be collected in a larger study so that their impact as covariates can be assessed.

The use of medical or surgical treatments for PDA and the use of postnatal steroids were identified during trial design as being treatments that could impact on the enrolled infants' respiratory outcomes. These treatments are used to improve a ventilator-dependent infant's lung function and aim to facilitate extubation. It was thought that their use would improve the hazard risk of infants reaching the 'success' criteria. As such the case record forms were designed to record the use of these interventions. The SAP identified surgical ligation of a

PDA and the use of postnatal steroids *a priori* as potentially influential covariates that would be analysed by univariable and multivariable analyses.

Univariable analyses appeared to show that these covariates led to a reduced hazard risk in the time to reach the 'success' criteria. This appeared to imply that they increased the duration of time taken for an infant to be ready for extubation. However, only six infants received a PDA ligation and only six received postnatal corticosteroids. These infants all required prolonged periods of ventilation. Given the small numbers of infants receiving either treatment, these results reflect the practice in this unit that these treatments were only considered for infants with severe lung disease. A larger trial may show different results. However, this also emphasises that the use of these treatments in a larger multi-centre trial would need to have clear, pre-defined specifications to minimise bias caused by differing practices.

7.5.5 The challenges of analysing data on an intention-to-treat basis

The challenges of defining an 'intention-to-treat' approach to data analysis was emphasised by this trial. The trial's protocol and SAP stated that statistical analyses would be carried out on an intention-to-treat basis for all infants for whom consent was obtained. Specific 'intention-to-treat' scenarios identified *a priori* in the protocol or SAP included those listed below.

- Infants for whom a protocol deviation occurred.
- Ineligible infants.
- Infants who received postnatal corticosteroids to facilitate extubation (allowed as a concomitant therapy and specified *a priori* as a potentially influential covariate).
- Infants who underwent surgical PDA ligation to facilitate extubation (allowed as a concomitant therapy and specified *a priori* as a potentially influential covariate). This involved a treatment to facilitate extubation and also required transfer to a cardiothoracic centre for an operation during which different modes of ventilation were used. The periods during which they received other modes of ventilation were included in the time-to-event analyses for primary and secondary outcomes.

- Infants who had an unplanned extubation and remained extubated for at least 24 hours (specified *a priori* in the definition of the primary outcome measure).

The points mentioned below were not specified *a priori* as those requiring intention-to-treat analysis but which were identified as such during the course of the trial.

- Infants who were extubated at the discretion of the treating clinician before reaching the ‘success’ criteria, either to avoid hypocarbia or to avoid prolonged ventilation (not specified in the protocol but permitted during the trial to maintain patient safety as part of a pragmatic protocol).
- Infants who received pressure-limited ventilation (PLV) at the discretion of the treating clinician. The use of ‘other non-trial modes of ventilation’ (which includes PLV) was included as a protocol deviation and monitored as part of compliance monitoring.

Data on the above events were collected for every infant for whom they occurred. These data are presented in Chapter 4 Results in the sections on compliance (Section 4.9), serious adverse events (Section 4.15) and secondary outcome measures (Section 4.12)

Only one infant was withdrawn from the trial after consent was obtained. The details of this are described in Section 4.2.6 of Chapter 4 Results. After randomisation had been undertaken and consent had been obtained, this infant was found to have an underlying congenital condition that intrinsically affected his/her respiratory system. This meant that (s)he was found, retrospectively, to meet the ineligibility criteria for the trial although this had not been known at the time of randomisation and consent.

The research team discussed this carefully and decided to exclude this infant from all data analyses. This decision was made because this infant’s underlying condition made him/her inherently different from the rest of the trial population. The aim of this pilot trial was to evaluate the effect of VG and VCV on the primary outcome in a target population. The target population was preterm infants whose principal need for ventilation was RDS. Although this infant did have RDS after birth it is possible that the initial requirement for mechanical

ventilation was due to the underlying congenital condition. Certainly this infant's ongoing need for mechanical ventilation was due to the underlying condition. Not only was the infant inherently different from the target population but his/her underlying condition influenced his/her interaction with the trial intervention and led to a prolonged course of ventilation. Had this infant's data been included in the analysis, the effects of this interaction would have impacted on inferences drawn from the trial's data.

Therefore the decision to exclude this infant's data from the analyses was a justified protocol deviation for this pilot trial (Giangregorio et al., 2015). The analysis undertaken was in keeping with a modified intention-to-treat analysis (Sianani, 2010; Gupta, 2011).

7.5.5.1 Addressing intention-to-treat challenges

In the strictest sense, undertaking intention-to-treat analyses involves analysing complete datasets from all participants randomised into a trial (Lamb et al., 2015). Data are analysed according to the arm to which the participant was randomised, regardless of whether the participant received the intervention or not.

There are several reasons for advocating a strict intention-to-treat approach to data analysis. These include aiming to:

- maintain the balance of prognostic baseline characteristics achieved through randomisation (Gupta, 2011; Sedgewick, 2015),
- minimise selection bias and manipulation of data (Gupta, 2011),
- encourage transparency and accountability (Gupta, 2011; Fergusson et al., 2002),
- reflect 'real life' events, in that patients who receive interventions outside a trial do not interact with these interventions in a protocolised manner (Gupta, 2011),
- achieve statistical power by ensuring that the sample size is maintained (Wertz, 1995)

As a result, a strict intention-to-treat approach minimises Type 1 errors and improves the validity and generalisability of the trial (Gupta, 2011, Fergusson et

al., 2002). Ideally, a strict intention-to-treat approach should be adhered to in all definitive trials (Sedgewick, 2015).

However there are difficulties in interpreting the results of this approach in early phase trials (Fergusson et al., 2002). Datasets may not be complete and missing data may either positively or negatively affect the intervention's impact on the outcome (Sainani, 2010). Some participants may not have received the intervention in full or even at all. Some participants may die or withdraw from the trial, meaning that their data are censored or incomplete. Factors that reduce compliance with the trial protocol can reduce the validity of the data ascribed to the interventions. Despite these challenges, it is considered good practice in a definitive trial to analyse data from all participants who have been formally randomised and enrolled (ICH Harmonised Tripartite Guideline E9, 1988).

A counter-argument to a strict intention-to-treat approach is that the analyses and results do not measure or reflect what they were intended to. Analysing all participants, regardless of the events that they encountered during a trial, has a dilutional influence on the effect of the interventions (Gupta, 2011). This can lead to Type 2 errors (Gupta, 2011; Fergusson et al., 2002). Different approaches have been described such as the modified intention-to-treat analysis (Gupta, 2011) and per protocol analysis (Sedgewick, 2015).

There are limitations to the decision to exclude one infant's data from The VoluVent Trial's analysis. It could have introduced subjective bias, particularly as this was an unmasked trial. The impact of excluding one infant from a small trial population could introduce a proportionately greater bias than exclusion of one infant from a large trial. In a pilot trial such as this, a modified intention-to-treat approach is acceptable because the aim of a pilot trial is to explore the effect of the interventions on a target population. In a larger definitive trial, a modified intention-to-treat analysis could lead to bias because exclusion of some participants' data interferes with the prognostic balance achieved through randomisation (Gupta, 2011; Fergusson et al., 2002).

The above challenges highlight the need to include a detailed definition of the intention-to-treat approach in a trial's SAP prior to data analysis and, preferably, prior to any data collection. Version-controlled SAPs can then be updated to

reflect unexpected events that may challenge the definition of intention-to-treat. In a pilot trial, a modification to the definition of intention-to-treat may be justified. However, in a large definitive trial, the original intention-to-treat definition should be adhered to for the reasons listed above. Modification to a strict intention-to-treat analysis can cause subjective bias (Gupta, 2011). Modified intention-to-treat or per protocol analyses can be acceptable as pre-defined secondary analyses within definitive trials.

Despite the above points, a definition of 'intention-to-treat' as the analysis of data from all enrolled participants can be relatively straightforward for trials using prospective consent. In such trials, consent is obtained before participants are randomised. However, the use of deferred consent introduces new challenges regarding the definition and implementation of intention-to-treat analysis. The VoluVent Trial highlighted examples of these challenges.

7.5.5.2 Effect of deferred consent on the definition of intention-to-treat

The introduction of deferred consent in The VoluVent Trial emphasised the impact that a consent method can have on defining and implementing an intention-to-treat approach. Twenty-nine infants were randomised but not enrolled because consent was not obtained. In line with good practice, these infants are accounted for in the CONSORT diagram (Figure 4-1) (Schulz et al., 2010; Fergusson et al., 2002). Obtaining written consent was one of the inclusion criteria for the trial. As consent had not been obtained from these infants' parents no data were collected or analysed. These infants (described in Section 4.2.5 of Chapter 4 Results) included:

- those whose parents declined consent,
- those whose parents were not approached or were not present in the unit before the consent deadline,
- those who were randomised but shortly afterwards found to have an anatomical congenital anomaly consistent with exclusion criteria,
- those who were randomised in error when being intubated after 24 hours of age (and therefore not meeting inclusion criteria).

These infants were balanced between groups; 14 had been randomised to VG and 15 had been randomised to VCV. This minimised the prognostic imbalance

that could have affected the trial population. This is reassuring given the small sample size in this trial. Such a balance between groups would be expected in a large trial but in a small trial, it is possible that lack of deferred consent may cause unequal allocation of interventions to the enrolled population.

As demonstrated above, a strict intention-to-treat approach (Lamb et al., 2015) is difficult to apply to trials using deferred consent. It is likely that there will always be some participants randomised but not enrolled. For example, the decision by parents to decline consent should never be overruled (General Medical Council, 2007) and data from those infants cannot be used. Infants who are randomised but then found, before consent is sought, to have diagnoses consistent with the exclusion criteria also cannot be enrolled.

However there are strategies to optimise the intention-to-treat approach that could be used for other infants who are randomised but not enrolled.

Seeking consent: Lack of consent because parents are not approached could be addressed by improving consent practices amongst the clinical or research teams. Lack of consent because parents have not arrived at the hospital before the consent deadline could be addressed by considering a different consent deadline. This may be possible in many trials but would have to be carefully considered. Extending a consent deadline too long may be perceived as withholding information from parents.

Infants randomised in error: Two infants were randomised but not enrolled because they had been intubated after 24 hours of age. In both cases the infants were otherwise similar to the trial population and they both had RDS. In such cases, advice could be sought from the ethics committee about whether to enroll them and include their data in analyses, or whether to exclude them from analyses (Fergusson et al., 2002). However, the consent deadline may not leave enough time to seek this advice, again highlighting how deferred consent can impact on adherence to a particular intention-to-treat approach.

Infants who died before consent was sought: Two infants were randomised appropriately but died before consent could be sought from parents. These parents were not approached with information about the trial and data on these infants were not collected. However, it is possible that bereaved parents can be offered the opportunity for their infants' data to be used in analyses. Qualitative

research has revealed that some bereaved parents would want the opportunity to consider giving consent for their infants' data to be used for analysis (Woolfall et al., 2014; Furyk et al., 2017). The approach and its timing would have to be carefully considered and individualised for each family.

Harron et al. (Harron et al., 2015) reported the use of deferred consent in a trial comparing different types of central venous catheter in a paediatric intensive care unit (PICU) (Gilbert et al., 2016). They discuss the challenges in seeking consent from bereaved parents but describe how it can be achieved. They highlight the important point that exclusion of such children from data analysis can reduce the validity and generalisability of an emergency interventions trial. They suggest that ethics committees should consider approving the use of data from such children without seeking consent, a suggestion also made by Jansen and colleagues (Jansen et al., 2007; Jansen et al., 2010). However, opinions on such a suggestion should also be sought from other stakeholders, including parents, children, young people, journal editors, and funders.

The above strategies may improve enrolment but it is likely that there will always be some infants who are randomised but not enrolled. The negative impact that this may have on the balance of prognostic covariates between groups would need to be accepted as a limitation in a trial using deferred consent. In a large trial, any imbalance is likely to be minimal. However, in a small trial the impact may be greater. One final strategy to address this would be the use of adaptive randomisation (Altman et al., 2005). With this strategy, as the trial proceeds, the overall balance of randomisation is maintained across treatment groups in eligible patients for whom consent is obtained. The original sample size would also need to be achieved in order to maintain power.

Experience gained through The VoluVent Trial can be used to plan a larger trial and the above strategies could be included prospectively in the trial protocol and SAP. An imbalance in randomisation would need to be monitored at pre-defined time points by a Data and Safety Monitoring Committee.

7.6 Other challenges

There were certain challenges encountered during the trial that were either unexpected or that could not be controlled for within the trial protocol. These challenges are described here.

7.6.1 Recruitment

The recruitment graph shown in Figure 4-2 demonstrates that, during the entire recruitment period, there were fewer eligible infants than expected. This, combined with the unforeseen problems in obtaining prospective parental consent during the first four months of the trial, meant that recruitment took five months longer than anticipated. Part of the process evaluation for a pilot trial is to identify and explore these unanticipated challenges. However, in a larger definitive trial, robust site feasibility assessments would be required prior to recruitment to ensure that recruitment targets could be achieved.

7.6.1.1 Use of non-invasive ventilation

The main reason for the reduction in the number of ventilated infants was due to the increase in the use of non-invasive ventilation (NIV) at the trial site in recent years. Such modes include CPAP and HHFNC. This reflects similar changes in practice in neonatal units throughout the world (Courtney, 2015). At the trial site itself, this change in practice may also have been influenced by the previous RCT run at the site that compared two modes of NIV in infants born between 28 and 31+6 weeks' gestation (Wood et al., 2013). The clinical team was familiar with, and had expertise in, the use of NIV in such infants since 2009. As such the use of NIV, and in particular the use of CPAP, in moderately and very preterm infants was embedded in routine care at the trial site.

7.6.1.2 Consent declined

Amongst those infants who were ventilated and therefore eligible, the lower than anticipated recruitment rate could be explained by a number of reasons. Figure 4-1 shows the CONSORT diagram for the trial, the numbers of infants not enrolled and the reasons for non-enrolment. Before the use of deferred consent, nine sets of parents declined prospective consent. After the introduction of deferred consent, 11 sets of parents declined deferred consent. Parents were not asked for their reasons for declining participation as this was felt to be inappropriate at such a stressful time in their lives. However, seeking information on such parental decisions is vital to improve the design of future trials. Consent being declined is likely in all research studies. Understanding parental reasons for declining consent may enable researchers to improve

parental experiences of being approached about research studies. Recent qualitative research has studied various aspects of consent for emergency research (Woolfall et al., 2014; Furyk et al., 2017) but information on the reasons for declining parental consent is lacking. A qualitative study exploring this aspect of recruitment could be undertaken as an individual study or as a nested study within the design of a definitive RCT.

7.6.1.3 Availability of parents to discuss the trial

Sixteen sets of parents were not present at the trial site in time to discuss the trial before the consent deadline. All of these infants were outborn infants. Eight were admitted to the trial site before the introduction of deferred consent. At that time the protocol stated that prospective consent had to be given within 12 hours of intubation. The other eight infants were admitted after the introduction of deferred consent at which point consent had to be given within 36 hours of intubation.

There were other outborn infants whose parents had arrived at the unit within a few hours before the consent deadline. Some of these parents were approached by senior clinicians or researchers experienced in seeking consent, if it was considered to be appropriate. However, some of these parents declined trial information on the basis that they did not have enough time to consider it before the consent deadline.

Along with the difficulties in seeking informed consent appropriately and sensitively in a trial of emergency interventions, these data highlight another challenge in recruiting to such trials. Recruiting outborn infants can be more difficult than recruiting inborn infants due to logistical challenges. One such challenge is the length of time taken to transfer the infant and the parents to the trial site. Another includes the fact that outborn infants may receive treatments outwith the trial protocol before randomisation. In this trial, outborn infants received other modes of ventilation before reaching the trial site. This can make data more difficult to analyse as certain covariates, to which inborn infants have not been exposed, need to be accounted for.

However outborn infants must not be excluded from research studies just because of difficulties in recruitment. It is just as important to improve their clinical care and outcomes through research as it is in inborn infants. Including

outborn infants in a research study creates a more heterogeneous study population. This ensures that the trial population's generalisability. Prior to the introduction of deferred consent, the 33% of parents of ventilated infants could not be approached because they had not arrived at the trial site. After the introduction of deferred consent only 5% of parents could not be approached for this reason.

The change in consent method was a major strength of this study for several reasons. It enabled a longer time frame in which to seek consent which increased the number of parents of outborn infants who could be approached. Randomisation of eligible infants at the time of admission or intubation ensured that infants could start their allocated trial mode of ventilation immediately. In recruiting more outborn infants, we improved the generalisability of the trial population and the results.

7.6.2 Radiological criteria used for the definition of respiratory distress syndrome

The trial protocol gave a clear description of the clinical, radiological and biochemical criteria with which a diagnosis of RDS could be made prior to randomisation. However, during the trial it became clear that some of these criteria could not be confirmed before randomisation.

The majority of infants (63%) was intubated and received surfactant in the delivery room. Initially, the opinion of an independent Paediatric Radiologist was sought to provide baseline assessments of the radiological features of RDS on the infants' initial chest x-rays. The Radiologist was blinded to treatment allocation. However, the prior administration of surfactant to infants who were intubated before receiving their first chest x-ray meant that the radiological features of RDS were minimal in most chest x-rays. Therefore this procedure was abandoned as very few chest x-rays provided meaningful baseline information on the initial severity of RDS. This also meant that the radiological criteria specified in the protocol's definition of RDS could not be reliably used in many of the trial infants.

7.6.3 Missing maternal data

Table 4-2 demonstrates that some of the data about maternal characteristics were missing. This particular part of the data collection was most affected by missing data. Data were deemed to be missing if they had not been recorded in the infants' medical records. These data were likely to have been recorded in the maternal medical records and should have been recorded in the infants' records as part of standard care. However the trial consent forms only permitted the Principal Investigator access to infants' records and therefore data in maternal records could not be accessed.

A recent neonatal trial used consent forms that included a statement giving maternal consent for researchers to access maternal medical records (McGuire, 2016). Therefore, in this trial, mothers' signatures were always required on the consent forms even if married fathers have also provided consent for their infants to participate. This enabled the research teams to seek relevant information in the maternal records that was missing from the infants' notes.

In designing a larger definitive trial on VTV, use of consent forms that permit the research team access to maternal records would substantially reduce missing data. This would improve the generalisability of the trial and give greater validity to the data on prognostic factors.

7.6.4 Use of sedation

Administration of sedation to enrolled infants was permitted as part of concomitant medications although it had to be stopped prior to extubation. Sedative medications often reduce respiratory drive, thereby potentially decreasing the likelihood of successful extubation. Therefore, the research team specified that infants must not have a SBT if they had received any sedation within the previous six hours. The clinical team adhered to this instruction. The use of sedatives in ventilated infants is not routine practice at the trial site. They were only used in a small number of infants at the discretion of the clinical team if deemed necessary for individual patients.

7.7 Summary and future directions

The VoluVent Trial demonstrated that there is a potential difference between VCV and VG in preterm infants, with those receiving VG being ready for

extubation sooner than those receiving VCV. The data from this trial are clinically relevant. As an example of a complex interventions study, The VoluVent Trial highlighted many methodological, procedural and clinical challenges that arise when undertaking research in an intensive care setting. The data and experiences gained from this trial can be used to plan a larger, definitive study. Recommendations for planning such a study are discussed in Chapter 8.

Chapter 8 Conclusion

This thesis described the use of a complex interventions trial to compare two emergency interventions in a neonatal intensive care setting. This was a randomised controlled trial called The VoluVent Trial (ISRCTN 04448562.)

Volume-targeted ventilation (VTV) is used in neonatology with the aim of limiting volutrauma and ventilator-associated lung injury (VALI) in ventilated newborn infants. It is associated with improved outcomes in newborn infants when compared with pressure-limited ventilation (PVL) (Klingenberg et al., 2017). Many of these outcomes are clinical manifestations of VALI, such as bronchopulmonary dysplasia (BPD) and pulmonary air leak. Others are indirect measures of the likelihood of VALI, such as duration of ventilation. The recently updated Cochrane review (Klingenberg et al., 2017) reported that the evidence favouring the use of VTV over PLV is now even stronger. The authors reiterated their recommendation that future research should include comparisons of different modes. The VoluVent Trial (ISRCTN 04448562) is the first and, to date, the only trial to compare two modes of VTV in ventilated preterm infants with respiratory distress syndrome.

The VoluVent Trial was a complex interventions trial comparing two emergency interventions within a neonatal intensive care setting. These interventions, volume-controlled ventilation (VCV) and volume guarantee (VG), are already in clinical use and this was, therefore, a comparative effectiveness trial. This pilot trial showed that infants receiving VG were ready for extubation faster than infants in the VCV group with a median difference of 13 hours. This clinically relevant result shows that a larger trial is required to provide a definitive result.

The VoluVent Trial also showed that future research should focus on ascertaining whether particular VTV modes benefit particular sub-groups of infants. The longer an infant is ventilated, the more their underlying lung condition changes and the more likely it is that their ventilation requirements will change (Keszler et al., 2009; Hunt et al., 2018). Therefore one remaining gap in knowledge is how to choose a VTV mode depending on the infant's gestational age and underlying pathology. In this trial, there was a marked difference in the duration of time taken to be ready for extubation in infants born at 28 – 33+6 weeks' gestation compared with those born at <28 weeks' gestation. Those

born at 28 – 33+6 weeks' gestation were ready for extubation much earlier than those born <28 weeks' gestation. The use of VG appeared to benefit infants in the more mature group. The use of VCV appeared to favour the more extremely preterm infants. These results provide useful data with which to plan a larger trial in order to answer these questions.

A process evaluation is essential when undertaking a pilot trial (Craig P. et al., 2008) and the ancillary study formed part of this process evaluation. Analysis of continuous airway pressure data sampled with every breath and at 100Hz closely matched the manual recordings of mean airway pressure values documented once every hour by neonatal nurses. This validated the primary outcome for this trial. It also provides unique data that validate the use of manual hourly recordings of mean airway pressure in neonatal intensive care.

The VoluVent Trial also demonstrated the challenges that can arise when investigating complex interventions in a complex environment. These included challenges with recruitment, obtaining informed consent, co-enrolment, statistical analysis considerations and clarifying an intention-to-treat definition. The strategies used to respond to these challenges included the use of deferred consent, a detailed SAP and a trial oversight review. These strategies provided useful information on how best to plan a larger, definitive trial.

The experience and data gained from The VoluVent Trial provide a set of recommendations that can be used when planning a larger neonatal trial on VTV. These recommendations are listed below.

Recommendations for a larger trial

1. Use the data from this pilot trial to determine a sample size that would provide definitive results for the whole population. Using statistical expertise, consider the feasibility of aiming for sample size that would provide significant results for sub-groups of infants, such as those of different gestational age groups.
2. Consider using a 'censor-point' for the primary outcome, after which all data would be censored. For example, data on only the first 96 hours could be analysed for the primary outcome. Data from infants who had not yet met the 'success' criteria by that point would be censored. This

would then enable analysis of the primary outcome to focus on infants with acute surfactant deficiency. Analysis of data beyond 96 hours could form part of the secondary outcome data but would provide a useful subgroup for analysis as infants ventilated longer than 96 hours tend to have changing lung pathology.

3. Include a request on the consent form that would permit researchers trial-specific access to maternal medical records.
4. Use deferred consent and include a nested qualitative study to obtain data on parents' experiences of this method of consent in the neonatal intensive care setting.
5. Consider a qualitative research study prior to undertaking a larger trial to ascertain the views of parents, ethics committee members, clinicians, researchers and other stakeholders on deferred consent and, in particular, on how and whether to seek consent for infants who die before consent is sought.
6. In the context of deferred consent, include a clear definition of the intention-to-treat approach in the protocol and SAP. Use the experiences from this trial to aim to ensure that as few randomised infants as possible are excluded from analysis. Data from infants whose parents do not give consent cannot be used. However, data from infants randomised in error or from those with congenital anomalies could potentially be used. These circumstances could be prospectively agreed with the ethics committee prior to starting the trial. Alternatively, it might be possible to include these infants in analysis if a strategy for seeking urgent advice from the ethics committee could be agreed upon.
7. Ensure that a Data Safety Monitoring Committee monitors the impact of deferred consent on the balance of randomisation for enrolled infants to ensure that a significant imbalance does not occur.
8. Clearly express strategies for co-enrolment in order to ensure that all parents are offered the choice of participation in multiple trials but are not burdened by it.
9. If a multi-centre trial is undertaken aim to ensure that the same devices are used in as many centres as possible. This may not be feasible in

which case a pragmatic approach could be considered in which different devices are used as long as the same modes are used.

10. Consider specifying clear criteria for the use of postnatal corticosteroids and surgical ligation of patent ductus arterioses. These criteria would standardise secondary outcomes. However, obtaining agreement on such criteria might be difficult in a multi-centre trial and a pragmatic approach may have to be considered. This could include analysing these variables as potentially influential covariates, as was done in this trial.
11. Use software such as the VOXP Research Data Collector to obtain mechanistic data on how the delivered tidal volumes differ between VCV and VG. Such data would be important in ascertaining the actual tidal volumes, and the stability of the tidal volumes, that are delivered to ventilated infants.

The VoluVent Trial has shown a clinically relevant difference between VCV and VG that appears to favour VG in preterm infants and, potentially, in the subgroup of infants born at 28 – 33+6 weeks' gestation. The recommendations above can be used to plan a larger trial to provide definitive results.

Chapter 9 Appendices

Appendix 9.1 Ethical approval from the North East-York Ethics Committee



NRES Committee North East - York

Room 002
TEDCO Business Centre
Viking Business Park
Rolling Mill Road
Jarrow, Tyne & Wear
NE32 3DT

Telephone: 0191 4283563

03 July 2013

Dr Helen Chitty
South Tees Hospitals NHS Foundation Trust
Neonatal Unit, The James Cook University Hospital
Marton Road
Middlesbrough
TS4 3BW

Dear Dr Chitty

Study title: A Randomised Controlled Trial Comparing Two Methods of Providing Volume-Targeted Ventilation in Preterm Infants with Respiratory Distress Syndrome: Volume Guarantee ® versus Volume-Controlled Ventilation

REC reference: 13/NE/0182

Protocol number: N/A

IRAS project ID: 121261

Thank you for your letter dated 26 June 2013. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 20 June 2013

Documents received

The documents received were as follows:

Document	Version	Date
Covering Letter		26 June 2013
REC application	Version 3.5 updated	21 June 2013

Approved documents


The final list of approved documentation for the study is therefore as follows:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Covering Letter		22 May 2013
Covering Letter		26 June 2013
GP/Consultant Information Sheets	Version 1	18 May 2013
Investigator CV	Helen Chitty	18 May 2013
Other: CV	Dr Sunil Sinha	20 May 2013
Other: CV	Dr Win Tin	23 April 2013
Other: Transfer Letter	Version 1	18 May 2013
Other: Short Summary	Version 2	18 May 2013
Other: Peer review email and reply		21 May 2013
Participant Consent Form	Version 6	18 May 2013
Participant Consent Form: Non Eligible Babies	Version 6	18 May 2013
Participant Information Sheet	Version 6	18 May 2013
Protocol	Version 6	18 May 2013
REC application	Version 3.5 updated	21 June 2013

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

13/NE/0182	Please quote this number on all correspondence
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Yours sincerely



Mrs Helen M Wilson
Committee Co-ordinator

E-mail: nrescommittee.northeast-york@nhs.net

Copy to: Mrs Julie Rowbotham, South Tees Hospitals NHS Foundation Trust

Appendix 9.2 Approval from The South Tees Hospitals NHS Foundation Trust's Research and Development Department (trial sponsor)



Research & Development / Academic Division
Academic Centre
The James Cook University Hospital
Marton Road
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TS4 3BW

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Tel: 01642 854089

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8th July 2013

Dr. Helen Chitty
Clinical Research Fellow
Neonatal Unit,
The James Cook University Hospital
Marton Road
Middlesbrough
TS4 3BW

Dear Dr Chitty

Re: 2013018 - A Randomised Controlled Trial Comparing Two Methods of Providing Volume-Targeted Ventilation in Preterm Infants with Respiratory Distress Syndrome: Volume Guarantee versus Volume-Controlled Ventilation

Your project was reviewed and approved by Research and Development on 8th July 2013.

The protocol and the following locally adapted documents have been reviewed and approved:

Document	Version	Date
Protocol	V6	18 May 2013
Participation Information Sheet	V6	18 May 2013
Participant Consent Form	V6	18 May 2013
Participant Consent Form: Non Eligible Babies	V6	18 May 2013
Short Summary	V2	18 May 2013
GP/Consultant Information Sheets	V1	18 May 2013
Transfer Letter	V1	18 May 2013

South Tees Hospitals NHS Foundation Trust manages all research in accordance with the requirements of the Research Governance Framework. As a researcher working in the Trust you must comply with all reporting requirements, systems and duties of action put in place by the Trust to deliver Research Governance. You are expected to read and

familiarise yourself with conditions of approval as well as Trust research SOPs in relation to your project.

For Trust sponsored studies it is the responsibility of Principal Investigators to adequately cover the on-going costs of their project. In addition to the costs of conducting the research, the following costs should also be considered:

- Monitoring
- Archiving

Enclosed are labels to be affixed to the front of Patient notes to indicate they are taking part in a clinical trial/study/registry. These are the only labels that should be used and any issued from another source should be discarded. Do not put the name of the trial on the label; the seven digit project ID referenced above should be used. If you require additional labels, please contact R&D.

If the R&D Department can be of any further assistance, please do not hesitate to contact us.

Kind regards.



Mr A Owens
Research & Development Director
GMC 3485934

Cc Professor Sunil Sinha
Consultant Neonatologist and Professor of Paediatrics and Neonatology
Paediatrics/Neonatal Medicine
The James Cook University Hospital

Appendix 9.3 Statistical Analysis Plan

A Randomised Controlled Trial Comparing Two Methods of Providing Volume-Targeted Ventilation in Preterm Infants with Respiratory Distress Syndrome:

Volume Guarantee® Ventilation versus Volume-Controlled Ventilation

Statistical analysis plan

1. RECRUITMENT AND RANDOMISATION

1.1 Recruitment

No planned interim analysis of data was specified in the trial protocol. However an analysis of data by a trial oversight advisor is being planned. Monthly recruitment data is available. The data will be locked when all secondary outcome data has been obtained (which is likely to occur after the final patient has been discharged from hospital).

1.2 Randomisation

Infants are stratified *a priori* into two groups according to gestational age at birth; <28 completed weeks' of gestation and 28 – 33⁺⁶ weeks' gestation. Assignment to either the volume guarantee mode or volume-controlled mode will be generated using block randomisation and serially numbered sealed opaque envelopes, which were prepared by a person independent of the trial. The person randomising an infant into the trial picks the top envelope from the box that corresponds to the infant's gestational age at birth. Infants are randomised on admission to the neonatal unit (if intubated prior to admission) or at the time of intubation (if intubated after a period of time on continuous positive airway pressure support). If, on admission, extubation of the infant appears imminent he/she will not be randomised.

It is expected that there will be similar numbers of infants in each intervention group within the two strata. It is expected that there will be a greater number of infants in the '<28 weeks' gestation' group than in the '28 – 33⁺⁶ weeks' gestation' group as the former group are more likely to be managed with mechanical ventilation via an endotracheal tube rather than non-invasive methods of respiratory support. The numbers of infants randomised to each intervention group will be made available to the trial oversight advisor and at the end of the trial.

1.3 Ineligible Patients

Statistical analyses will be carried out on an intention-to-treat basis for all infants for whom consent was obtained. Infants will be retained in their randomised intervention groups which will include those for whom a protocol violation occurred and ineligible patients. Ineligible patients are classed as those randomised patients who are found to subsequently not adhere to the eligibility criteria of the trial. The number of ineligible patients and reasons for ineligibility will be reported and a sensitivity analysis may be conducted and reported if the number of ineligible patients is excessive.

2. DATA QUALITY

2.1 Forms Returned

Data are collected using case report forms (CRF). Completion rates for each CRF will be reported.

2.2 Follow-Up

The number of infants who do not reach the primary outcome before death or transfer to another hospital will be reported. These infants will not be excluded from the analysis but their data will be censored at the duration of ventilation at which death or transfer to another hospital occurred.

3. STUDY POPULATION

3.1 Baseline Patient Characteristics

Demographic, antenatal and clinical baseline characteristics and trial stratification factors at randomisation will be compared across treatment groups descriptively. Descriptive statistics will be tabulated by treatment group and overall. Significance testing will not be carried out due to the randomised nature of the study. Mean values will be used, as indicated in the tables below, for normally distributed data. Median values will be used for non-normally distributed data.

Baseline characteristics for comparison will include:

Table 3.1 Maternal demographic and antenatal details

Characteristics	VG	VCV	Total population
Maternal age, years, mean (SD)			
Maternal ethnicity, White British, n (%)			
Multiple pregnancy, n (%)			
At least one dose of antenatal steroids received, n (%)			

Number of doses of antenatal steroids received			
<ul style="list-style-type: none"> • none, n (%) • 1 dose, n (%) • ≥2 doses, n (%) 			
PPROM (>18 hours), n (%)			
Duration of PPRM, hours, mean (SD)			
PPROM before 23 weeks' gestation, n (%)			
GBS isolated in this pregnancy, n (%)			
Maternal chorioamnionitis, n (%)			
Maternal fever > 37.5°C, n (%)			
Antenatal antibiotics, n (%)			
Intrapartum antibiotics (>4 hours before delivery, n (%)			
Any positive maternal culture, n (%)			
Antepartum haemorrhage, n (%)			
Pregnancy-induced hypertension, n (%)			
Pre-eclampsia, n (%)			
Eclampsia, n (%)			
Maternal diabetes, n (%)			

PPROM, prolonged preterm rupture of membranes; GBS, group B streptococcus

Table 3.2 Delivery details for all infants

Characteristics	VG	VCV	Total population
Completed weeks of gestation at the time of delivery, mean (SD)			
Birth weight, g, mean (SD)			
Small for gestational age, n (%)			
Male gender, n (%)			
Female gender, n (%)			

Born at the trial site, n (%)			
Labour before delivery, n (%)			
Born by LSCS, n (%)			
Breech presentation, n (%)			
Multiple birth, n (%)			
Intubated in the delivery room, n (%)			
Apgar score at five minutes, mean (SD)			
Age on admission to trial site, minutes, mean (SD)			
First recorded admission temperature, °C, mean (SD)			

LSCS, lower segment caesarean section; °C, degrees Celsius

Table 3.3 Delivery details for infants born at <28 weeks of gestation

Characteristics	VG	VCV	Total population
Completed weeks of gestation at the time of delivery, mean (SD)			
Birth weight, g, mean (SD)			
Small for gestational age, n (%)			
Male gender, n (%) Female gender, n (%)			
Born at the trial site, n (%)			
Labour before delivery, n (%)			
Born by LSCS, n (%)			
Breech presentation, n (%)			
Multiple birth, n (%)			
Intubated in the delivery room, n (%)			
Apgar score at five minutes, mean (SD)			
Age on admission to trial site, minutes, mean (SD)			

First recorded admission temperature, °C, mean (SD)			
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LSCS, lower segment caesarean section; °C, degrees celsius

Table 3.4 Delivery details for infants born at 28 – 33+6 weeks of gestation

Characteristics	VG	VCV	Total population
Completed weeks of gestation at the time of delivery, mean (SD)			
Birth weight, g, mean (SD)			
Small for gestational age, n (%)			
Male gender, n (%) Female gender, n (%)			
Born at the trial site, n (%)			
Labour before delivery, n (%)			
Born by LSCS, n (%)			
Breech presentation, n (%)			
Multiple birth, n (%)			
Intubated in the delivery room, n (%)			
Apgar score at five minutes, mean (SD)			
Age on admission to trial site, minutes, mean (SD)			
First recorded admission temperature, °C, mean (SD)			

LSCS, lower segment caesarean section; °C, degrees celsius

Table 3.3 Outborn infants: clinical details prior to trial entry

Characteristics	VG	VCV	Total population
Level 1 referring unit, n (%)			
Non-invasive ventilation used at referring hospital, n (%)			
Duration of non-invasive ventilation at referring hospital, minutes, mean (SD)			
Mechanically ventilated at referring hospital, n (%)			
Age at intubation, minutes, mean (SD)			
Number of doses of surfactant given at referring hospital, mean (SD)			
Number of doses of surfactant given in total, mean (SD)			
Duration of ventilation prior to starting trial mode of ventilation, minutes, mean (SD)			
Age on arrival at trial site, minutes, mean (SD)			
Age when starting trial mode, minutes, mean (SD)			

Table 3.4 Inborn infants: clinical details prior to trial entry

Characteristics	VG	VCV	Total population
Non-invasive ventilation used before intubation, n (%)			
Duration of non-invasive ventilation before intubation, minutes, mean (SD)			
Age at intubation, minutes, mean (SD)			
Number of doses of surfactant prior to starting trial mode, mean (SD)			
Number of doses of surfactant given in total, mean (SD)			
Mechanically ventilated before randomisation and start of trial mode, n (%)			
Duration of mechanical ventilation prior to starting trial mode, minutes, mean (SD)			

Age when starting trial mode, minutes, mean (SD)			
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Table 3.4 Comparison of characteristics of inborn infants and outborn infants

Characteristics	Inborn infants	Outborn infants
Completed weeks of gestation at the time of delivery, mean (SD)		
Birth weight, g, mean (SD)		
Gender: Male, n (%) Female, n (%)		
Singleton, n (%)		
Received non-invasive ventilation before intubation, n (%)		
Duration of non-invasive ventilation before intubation, minutes, mean (SD)		
Age at intubation, minutes, mean (SD)		
Number of doses of surfactant given in total, mean (SD)		
Duration of ventilation prior to starting trial mode of ventilation, minutes, mean (SD)		
Age at start of trial mode, minutes, mean (SD)		

Table 3.5 Respiratory and ventilation parameters on initiation of the trial mode of ventilation

Parameters	VG	VCV	Total population
Mean airway pressure, cm H ₂ O, mean (SD)			
Peak inspiratory pressure, cm H ₂ O, mean (SD)			
Expired tidal volume, mls/kg, mean (SD)			
Minute volume, mls/minute, mean (SD)			
Fraction of inspired oxygen, mean (SD)			
Lung compliance			

3.2 Defining Populations for Analysis

The following sub-groups will undergo separate analyses:

- Infants born at <28 weeks' gestational age versus infants born between 28 and 33+6 weeks' gestational age (according to a priori stratification at the time of randomisation).
- Data from inborn infants (infants born in the trial hospital) will be analysed, with data from outborn infants (those born in other hospitals) excluded.

4. TREATMENT RECEIVED

Due to the nature of the trial interventions, treatment is not masked. The trial is a pragmatic one and designed to incorporate protocol treatment schedules with variations in clinical practice. Therefore some variations in treatment may occur and these will be reported as described below.

The following variations will be reported by each treatment group:

- The number of infants receiving the trial intervention only, and no other form of mechanical ventilation via an endotracheal tube.
- The number of infants receiving other forms of mechanical ventilation or non-invasive ventilation prior to randomisation.
- The use of high frequency oscillatory ventilation (HFOV) in infants who are deteriorating on the trial intervention. This is allowed as part of the trial protocol. The duration of time on the trial intervention prior to changing to HFOV and the duration of time spent on HFOV will be reported. If HFOV is used, the data will be analysed on an intention-to-treat basis.
- Infants requiring transfer to other hospitals whilst ventilated will not receive the trial intervention during transfer or at the receiving hospital. If they are not transferred back to the unit prior to meeting the primary outcome their data will be censored. If they are transferred back to the unit and subsequently go on to meet the primary outcome their data will be analysed on an intention-to-treat basis.
- The number of infants ventilated using the trial intervention for whom the primary outcome is not reached prior to extubation will be reported.
- The number of infants requiring more than one period of ventilation will be reported.
- The use of therapies that are likely to have an impact on the ability to wean ventilation will be reported by each treatment group. These include, but are not limited to, the use of steroid medication to facilitate extubation in ventilator-dependent infants and the use of medical and/or surgical treatment to facilitate closure of the ductus arteriosus. In these cases, data will be analysed on an intention-to-treat basis.

- The number of protocol violations, the number of infants for whom violations occur, and reasons for violation will be reported.
- The total duration of ventilation will be analysed as a secondary outcome along with other clinical outcomes related to respiratory status and prematurity as listed in the protocol.

5. SAFETY ANALYSIS

5.1 Expected serious adverse event (SAE) - expected serious adverse events that may reasonably be expected to occur in the infants in the study include:

- death
- bronchopulmonary dysplasia (chronic lung disease)
- requirement for re-intubation
- pulmonary air leak during mechanical ventilation, including pneumothorax, pneumomediastinum, pneumopericardium, pneumatocele, pulmonary interstitial emphysema.
- hypocarbia ($pCO_2 < 4.0kPa$)
- pulmonary haemorrhage
- necrotising enterocolitis
- intestinal perforation
- intracranial haemorrhage or focal white matter damage found on imaging
- persistent patent ductus arteriosus
- retinopathy of prematurity

These SAEs will not require immediate reporting but will be recorded prospectively in medical case notes and managed by the treating clinician in accordance with standard unit practice. Expected SAEs will be recorded prospectively on the case report forms and separate SAE forms and will be monitored and assessed for causality by trial investigators.

5.2 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A suspected unexpected serious adverse reaction is “A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question, as defined in the summary of product characteristics for that product in the case of a product with an authorisation, or in the investigator’s brochure relating to the trial in question in the case of any other investigational medicinal product.”

5.3 Reporting of adverse events

The total numbers of adverse events, and the numbers of infants affected by each adverse event, will be reported as specified in the trial protocol.

6. EFFICACY ANALYSIS

6.1 Definition and Calculation of Efficacy Outcome Measures

6.1.2 The primary outcome

Definition: This is the duration of ventilation (in hours) from starting the trial intervention until reaching the 'success criteria'. The 'success criteria' are reached when the mean airway pressure of $<8\text{cmH}_2\text{O}$ **AND** FiO_2 of ≤ 0.35 have been maintained for six consecutive hours followed by successful completion of a spontaneous breathing test. If there is an unplanned extubation after which the infant remains extubated for at least 24 hours, this will also be classed as "success" and results will be analysed on an intention to treat basis.

6.1.3 Time points for measurement of the primary outcome:

Most infants will receive only the allocated trial intervention and will reach the primary outcome as specified in the protocol. However, for some infants, there will be variations as described in Section 4 of this analysis plan.

The start of the trial intervention will be measured using one of two time points:

- For infants who are already ventilated on admission to the neonatal unit this is the time of admission to the neonatal unit as documented in the medical records.
- For infants intubated after admission to the neonatal unit, this is the time of surfactant administration as documented in the medical records.

The time points for reaching the 'success criteria' may vary. It is expected that most infants will reach the 'success criteria' and therefore the primary outcome. However, some infants will be successfully extubated without reaching the specified 'success criteria' or primary outcome. These two events are described below.

- If a successful spontaneous breathing test is completed, the time of completion of the test is the time at which the 'success criteria', and therefore the primary outcome, are met.
- If an infant has a planned or unplanned extubation prior to completion of a successful spontaneous breathing test, and remains extubated for at least 24 hours, the time of extubation as documented in the medical notes will be taken as the 'success criteria'. For these infants, this will be the point at which the primary outcome is met.

For some infants the primary outcome will not be reached. In these cases the data will be non-informatively censored. These include infants who:

- die before completion of a successful spontaneous breathing test,
- are transferred to another hospital before completion of a successful spontaneous breathing test.

The time-points for censoring data are the date and time of the last set of observations documented on the nursing observation chart.

6.2 Original sample design and size

This section describes how the sample size was determined when the trial was originally designed. In summary, the sample size was based on data reported in a study by Singh *et al* (2). In that paper the primary outcome data were reported as mean values. Therefore, when this current trial was being designed in 2013 parametric tests were used to calculate the sample size because the primary outcome data were reported as mean values (see section 6.2.1).

However, as this is a pilot trial, with the aim being to inform the design of a larger trial, an alternative method of statistical analysis is preferable. This is discussed in sections 6.2.3 and 6.3.2, and is based on the statistical methodology for randomised phase II trials described by Jung (3).

Please note that, for the current trial, **no** data have been analysed before this final version of the statistical analysis plan (version 9, dated 4th May 2016) has been completed and saved as a PDF document.

6.2.1 Determining the sample size

Data from two previous studies undertaken at the trial site (1,2) were used as references with which to determine the original sample size.

In the first of the two previous studies, VCV was compared with pressure-limited ventilation (PLV) in preterm infants with respiratory distress syndrome (1). Fifty infants (25 in each arm) weighing ≥ 1200 g were randomised to either VCV or PLV. Predetermined success criteria were used as primary outcome measures (time to achieve an alveolar-arterial oxygen gradient of <13 kPa or mean airway pressure of <8 cmH₂O, maintained for >12 hours). In the VCV group, the mean(SD) time taken to reach the success criteria was 65.5(55.7) hours. For infants in the PLV group the mean(SD) time was 125.8(131.8) hours, $p<0.001$.

In the second trial, Singh *et al.* (2) compared VCV and PLV in smaller and more premature infants using the same success criteria. One hundred and nine infants (57 in one arm and 52 in the other arm) born between 24 and 31 completed weeks' gestation and weighing between 600 and 1500g were recruited. Although there was no significant difference between the two groups in the time taken to meet the success criteria, infants assigned to VCV achieved the criteria faster than infants in the PLV group (mean time of 23 hours versus 33 hours respectively, $p=0.15$). A sub-group analysis showed that in infants weighing <1000 g, VCV significantly reduced the time taken to achieve the success criteria compared with PLV (mean time of 21 hours and 58 hours respectively, $p=0.03$).

We hypothesised that the time taken to achieve the 'success criteria' will be significantly lower using VG compared with VCV. The mean values in the previously published trials (1,2)

were both used to calculate the sample size, based on a 2-sided alpha of 0.05 and a power of 80% and using a reduction of 33% in the time taken to reach success criteria.

Table 6.1 Determination of the sample size using data from previous studies

	Sinha <i>et al</i> (1)	Singh <i>et al</i> (2)
Known mean value of time to reach success criteria in VCV group	65.6 hours	23 hours
Standard deviation of the known value	55.7	19.26
Reduction in time to reach success criteria (effect size)	33%	33%
Mean value if a 33% reduction in time to success criteria occurred in VG group	43.952 hours	15.41 hours
2-sided alpha	0.05	0.05
Power	0.8	0.8
Sample size	52 in each arm	51 in each arm

The data from Singh *et al*'s study (1) were used because those data more closely reflect current practice. Therefore, a sample size of 102 infants (51 in each arm) was needed to show a 33% reduction in the time taken to reach the success criteria from 23 hours in the VCV group to 15 hours in the VG group with a 2-sided alpha of 0.05 and a power of 80%.

6.2.2 Retrospective sample size calculation using non-parametric tests

The primary outcome data reported by Singh *et al.* (2) were reported as mean values and therefore, parametric tests were used to calculate the sample size for this trial. However, according to personal communication with Dr. Singh (23/04/2016), the data from his trial were not normally distributed. It is likely that the data from the current trial will be non-normally distributed, although this cannot yet be confirmed as the data have not yet been analysed.

A retrospective sample size calculation with a log-rank test was performed using the data reported by Singh *et al.* (2). The software used was Sample Size Tables for Clinical Studies Software Program, version 1.0, July 2008. The proportions were based on taking an end point of 48 hours on the Kaplan-Meier curve from the paper by Singh *et al.* (2) and comparing the associated cumulative survival points. At 48 hours, the cumulative survival in the VCV arm was approximately 0.05 and in the TCPL arm it was 0.15. If the number of events (number of infants reaching 'success criteria') in each arm is 52 (based on the original sample size calculation in my trial), power 0.8, allocation (randomisation) ratio 1:1, first proportion 0.05, second proportion 0.15 and significance level 0.05, the sample size would need to be 178.

6.2.3 Analysis of results using differences in response rates.

A different approach to statistical analysis of data from this trial is that described by Jung (3) for design of randomised phase II trials with a prospective control arm. This involves an

initial stage of research (Jung refers to this as the “single-stage” element which equates to a pilot trial) in which response rates to an intervention in the control arm and in the comparison arm are compared. If the difference between the response rates is sufficiently large that it reaches a pre-determined level at the end of that initial stage, the trial team then proceeds to a larger trial to aim for a definitive result. If the difference between the two arms is not sufficiently large and does not reach the pre-determined level it is unlikely that there is a difference between the two arms and the research is terminated.

Using this approach to interpret the data by Singh et al (2), the response rates can be defined as the proportion of infants who had reached the success criteria at a particular time point. According to the Kaplan Meier curve reported by Singh et al. (2), the cumulative survival (the proportion of infants that still had not reached the success criteria) at 48 hours was approximately 0.05 in the VCV arm and 0.15 in the TCPL arm. This also means that the proportion reaching the success criteria by 48 hours was 0.95 in the VCV group and 0.85 in the TCPL group. The sample size for that trial was 109, meaning that the response rate was approximately 85% of infants in the TCPL group and approximately 95% of infants in the VCV group at 48 hours. In terms of clinical relevance this means that approximately 10 more infants had met the success criteria by 48 hours in the VCV group compared to the TCPL group. This is an important clinical difference between the two groups.

We consider the methodology described by Jung (3) to be more appropriate for this current trial because, as a pilot trial, its aim is to inform the direction of a larger trial or body of research rather than provide a definitive result.

6.3 Statistical analysis of the primary outcome

6.3.1 Descriptive analysis of the primary outcome measure

The primary outcome data will be analysed for all enrolled infants on an intention-to-treat basis and results from the two treatment groups will be compared regardless of whether they received the allocated mode. Infants are stratified *a priori* at the time of randomisation into two groups; those born at <28 weeks of gestation and those born between 28 – 33+6 weeks of gestation. Data from both stratified groups will also be presented and described separately but will not be tested for significance.

The primary outcome data will be presented using time-to-event (time to ‘success’ criteria) Kaplan-Meier survival curves and reported as survival probabilities. These data are likely to be non-normally distributed. The mean value of the ‘area under the curve’ of the Kaplan-Meier survival distribution can be biased depending on whether the last patient has censored data or not. Therefore, if this is the case, data will be presented as medians with confidence intervals. Any normally distributed data will be presented as means with standard deviations and differences in means with confidence intervals.

6.3.2 Statistical significance and clinical relevance

A significance level of 0.15 has been chosen. This is acceptable for pilot trials that aim to inform the design of a larger trial rather than provide a definitive, statistically significant result. According to Jung (3), this significance level is reached assuming a 15% difference between the two groups in the time to reach the success criteria at 48 hours (see section 6.3.3).

6.3.3 Comparison of response rates between the two groups.

The prospective control arm is the VCV group and the comparison arm is the VG group. Using the approach described by Jung (3) for the first stage of a trial (the single-stage element or pilot trial) the response rate, or event rate, in each arm can be defined as the number of infants successfully reaching the success criteria (the primary outcome as defined in the trial protocol, version 9, dated 21/09/2014).

Using Table 1 in the paper by Jung (3), and assuming balanced allocation between groups, a sample size of 96 infants (48 in each arm) allows a response probability of 0.8 (80%) in the control arm (VCV group) and 0.95 (95%) in the comparison arm (VG group) to be observed with a significance level of 0.15 and a power of 0.8.

According to Jung (3) the primary decision to proceed to a larger trial after the pilot trial is based on observing a specific difference between the two arms. This difference is the difference in the number of responses (infants reaching the success criteria) between the two arms. Therefore, as stated in the paragraph above, if the number of infants who reach the success criteria at 48 hours in the VG group is at least 15% greater than that in the VCV group, there is a potential significant difference between the two groups that could be investigated further in a larger trial. If this size of difference is not observed then due consideration will be made to all secondary outcome measures in making a decision to proceed to a larger trial.

6.3.4 Analysis of confounding variables

A Cox proportional hazards model will be used to investigate the effects of confounding variables. Univariate analyses will be undertaken and results will be presented as hazards ratios with confidence intervals. The confounding variables likely to affect the primary outcome include

- the administration of maternal antenatal steroids prior to delivery,
- the administration of postnatal steroids to infants facilitate extubation,
- surgical management of a patent ductus arteriosus.

6.4 Statistical analysis of secondary outcome measures

The secondary outcome measures are:

Respiratory outcomes

- Total duration (in hours) of mechanical ventilation via an endotracheal tube until first extubation.
- Requirement for reintubation within 72 hours of extubation.
- Total duration (in hours) of mechanical ventilation via an endotracheal tube until successful extubation.
- Pulmonary air leak while receiving mechanical ventilation (including pneumothorax, pneumomediastinum, pneumopericardium, pneumatocele, and pulmonary interstitial emphysema)
- Number of episodes of hypocarbia during mechanical ventilation (defined as carbon dioxide tension of less than 4.0 kPa) requiring adjustment of ventilation.
- Total duration (in hours) of non-invasive artificial respiratory support including nasal continuous positive airway pressure (CPAP), bilevel nasal CPAP and high flow nasal cannulae.
- Number of infants requiring rescue treatment (high frequency oscillatory ventilation)
- Need for continuous or intermittent supplemental oxygen at a postmenstrual age of 28 days and 36 weeks' corrected gestational age.
- Bronchopulmonary dysplasia requiring home oxygen therapy or continuation of any form of respiratory support at home

Mortality

- Death before discharge from hospital

Neurological outcomes

- Severe intraventricular haemorrhage (grades 3 or 4 according to the Papile classification)
- Periventricular leukomalacia

Outcomes related to prematurity

- Retinopathy of prematurity requiring laser treatment
- Patent ductus arteriosus requiring medical or surgical treatment
- Necrotising enterocolitis (Bell stage 2 or greater)
- Intestinal perforation not due to necrotising enterocolitis
- Number of confirmed episodes of infection (positive cultures from blood and cerebrospinal fluid at a time when the infant showed clinical signs of infection)

6.4.1 Descriptive analyses of secondary outcome measures

Some secondary outcome measures consist of continuous data and others consist of binary data. Normally distributed continuous data will be presented as means with standard deviations and differences in means with confidence intervals if it is normally distributed.

For non-normally distributed data, medians and their inter-quartile ranges will be presented. Binary secondary outcome measures will be presented as percentages.

6.4.2 Further analyses of secondary outcome measures

Continuous data will be analysed using the unpaired t-test if they are normally distributed. A non-parametric test (such as Mann Whitney U test) will be used if the data are not normally distributed.

Binary data will be compared using chi-squared contingency table tests or a Fisher exact test and presented using odds ratios with confidence intervals. The effect of confounding variables will be investigated using logistic regression analyses and adjusted odds ratios.

6.5 Statistical software

Data will be input into electronic databases and coded by the Principal Investigator. The data will be downloaded into statistical software such as STATA/SPSS and analysed by the Principal Investigator.

7. SUBGROUP ANALYSIS

Any observed treatment effect will be investigated across identified prognostic subgroups and within stratification groups to identify the size of the effect and whether this is consistent across different subgroups. This is purely exploratory analysis and has not been powered to detect treatment differences within specific subgroups of patients. As such hazard ratios of the treatment effect within subgroups will be estimated without significance testing and presented graphically using forest plots. Tests of heterogeneity will be carried out to determine if any treatment effects differ substantially across subgroups.

Prognostic subgroups include:

- Infants born at <28 weeks' gestational age versus infants born between 28 and 33+6 weeks' gestational age (according to a priori stratification at the time of randomisation). Infants born at <28 weeks' gestation are described as extremely preterm infants whereas those born at 28 – 33+6 weeks' gestation are described as very preterm infants. This stratification has been undertaken because extremely preterm infants are more likely to require longer periods of mechanical or non-invasive respiratory support (which may affect their primary outcome data) and develop other complications of premature birth (which will affect their secondary outcome data) than very preterm infants. Although the study is not powered to detect differences between treatment groups in either group it will be important to know if there are any trends within the subgroups to determine whether further research targeting these specific groups is needed.
- Data from inborn infants (infants born in the trial hospital) will be analysed, with data from outborn infants (those born in other hospitals) excluded. This is because infants born in other hospitals are likely to have received modes of ventilation that are not under investigation in this study. Although data from outborn infants will be analysed on

an intention-to-treat basis as part of the main analysis, data from inborn infants will also be analysed separately to determine if there are trends towards any differences in outcomes when data from outborn infants are excluded.

8. STORAGE

Data will be processed and stored according to South Tees Hospitals NHS Foundation Trust's standard operating procedures as described in the trial protocol. Data will be coded before being analysed. No patient identifiable information will be used for coding or analysis or for any reports or publications.

REFERENCES

1. Sinha SK, Donn SM, Gavey J, *et al.* Randomised trial of volume controlled versus time cycled, pressure limited ventilation in preterm infants with respiratory distress syndrome. *Arch Dis Child* 1997;**77**:F202-F205.
2. Singh J, Sinha SK, Clarke P, *et al.* Mechanical ventilation of very low birth weight infants: is volume or pressure a better target variable? *J Peds* 2006;**149**(3):308-13.
3. Jung S-H. Randomized phase II trials with a prospective control. *Stat Med* 2008;**27**:568-583.

Appendix 9.4 Spontaneous breathing test data collection form

The VoluVent Trial

The Spontaneous Breathing Test (write the results on page 3)

When ventilation has been weaned and the Extubation Assessment Chart shows that the infant has had a mean airway pressure $<8\text{cmH}_2\text{O}$ and $\text{FiO}_2 \leq 35\%$ for 6 consecutive hours (with satisfactory blood gases and expired tidal volumes of $4.0\text{--}4.5\text{mls/kg}$), proceed to the Spontaneous Breathing Test.

The set rate on the ventilator (the 'back up rate') should be between 20 and 40 breaths per minute before the test. **Do not start the test if the set rate is higher than 40 breaths per minute.**

Performing the Spontaneous Breathing Test

1. Press the 'Mode' button on the left side of the ventilator. In the MODE SELECT window that appears select 'CPAP/PSV' and then select 'Pressure' APNEA MODE (see photo 1).

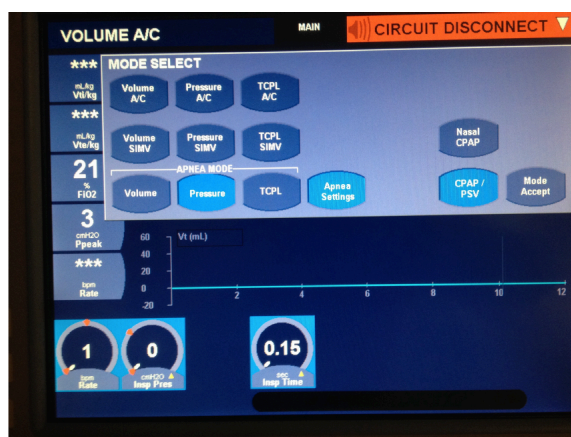


Photo 1

2. Next, select 'Apnea Settings' (photo 1)
3. At the bottom left corner of the screen, three dials will appear: Rate, Insp Press and Insp Time (see photo 1):
 - a. Turn the rate down to 1bpm.
 - b. Turn the Insp Press down to 0.
 - c. Turn the Insp Time down to 0.15 sec
4. Then select Mode Accept.
5. Ensure that (see photo 2 over page):
 - a. the PEEP is set at $5\text{cmH}_2\text{O}$
 - b. the PSV is set at $0\text{cm H}_2\text{O}$
 - c. the flow trigger is set at 0.2 litres



Photo 2

6. Ensure that continuous cardiorespiratory monitoring is maintained.

The infant is now receiving endotracheal CPAP!

7. Record the observations at the start of the test on the Spontaneous Breathing Test results page (page 3 of this document).
8. Observe the infant for 3 minutes and record the observations every minute on the results page.

9. Observe closely for these two events:

- a. bradycardia >15 seconds requiring IPPV
- b. oxygen saturations drop to 85% despite increasing FiO₂ by 15% (ie: FiO₂ is increased from 21% to 36%, or from 25% to 40%, etc.)

If one or both occur at any time during the test, stop the test and restart ventilation using the settings that the infant was on before the test.

10. After three minutes, the test has been successful if:
 - there is no bradycardia >15 seconds requiring IPPV or
 - the FiO₂ is no more than 15% higher than it was at the start of the test

If the test is successful

If the test has been successful the infant can be extubated immediately **if it is an appropriate time to do so**. If it is not an appropriate time to extubate the infant, restart ventilation using the settings that the infant was on before the test and extubate the infant as soon at the earliest appropriate opportunity.

If the test is not successful

If the test is not successful, or has to be stopped before the end of three minutes, restart ventilation using the settings that the infant was on before the test. Repeat the test after 6 hours as long as the mean airway pressure is <8cmH₂O and the FiO₂ is ≤35%.

The VoluVent Trial

Results (please complete all sections)

1. Patient's name _____
2. Today's date: _____
3. Type of ventilation during trial _____
4. Record the time and date at which the mean airway pressure was $<8\text{cmH}_2\text{O}$ and the $\text{FiO}_2 \leq 35\%$ for 6 consecutive hours (See Extubation Assessment Chart)
Date: _____ Time: _____

During the test, if you observe either of the following you must stop the test and restart ventilation:

- a. bradycardia >15 seconds requiring IPPV
- b. oxygen saturations drop to $<85\%$ despite increasing the FiO_2 by 15% (ie: FiO_2 21% at the start and then increased to 36%, FiO_2 25% at the start and then increased to 40% etc)

	Start of test	End of 1 minute	End of 2 minutes	End of 3 minutes
Time (use 24 hour clock)				
Heart rate (beats per min)				
Respiratory rate (breaths per minute)				
Oxygen saturations (%)				
FiO_2 requirement (%)				

5. At the end of three minutes:

- a. Is the heart rate stable?
- b. Are the oxygen saturations $>85\%$ with no more than a 15% increase in the FiO_2 ?

Column 1 Column 2

Yes No
Yes No

Go to qu 7
and 8

Go to
qu 9

6. **At the end of the test ensure that the Inspiratory Pressure limit is set back at $20\text{cmH}_2\text{O}$ (see the guides to using Volume Guarantee in the infant's trial pack).**
7. If the answers to question 5 are **all** in column 1, the infant can be extubated now **if it is an appropriate time to do so**.
Time of extubation: _____ OR Reason why extubation is delayed: _____
8. If the answers to question 5 are **all** in Column 1 **but it is not an appropriate time to extubate the infant**, restart ventilation and extubate the infant at the earliest appropriate opportunity. Time of delayed extubation: _____
9. If **any** of the answers to question 5 are in Column 2, restart ventilation and repeat the test 6 hours later if the mean airway pressure remains $<8\text{cmH}_2\text{O}$ and the FiO_2 remains $\leq 35\%$. Use another Spontaneous Breathing Test form to record the results of any further tests.

Appendix 9.5 Caring for an infant randomised to VCV

- 1) Written parental consent must be obtained within 36 hours of randomisation
- 2) Pick a sealed opaque envelope from box according to appropriate gestational age group. Write the infant's name and hospital number on the envelope **before** opening it.
- 3) Infant is allocated to volume assist-control mode.
- 4) Select ventilator settings:
 - a) Mode:
 - i) Select volume assist-control mode
 - b) Volume:
 - i) Use the volume dial to select a delivered volume that achieves a tidal volume of 4-6mls/kg in infants.
 - Initially set the volume at 12mls/kg to deliver 4-6mls/kg of inspired tidal volume.
 - Titrate the delivered tidal volume up or down **to aim to keep the expired tidal volume between 4-6mls/kg.**
 - c) Set the positive end expiratory pressure (PEEP) at 4-6cmH₂O.
 - d) Set the back up rate at 40 per minute.
 - e) Adjust the flow to aim for an inspiratory time at 0.35 seconds.
 - f) Set the assist sensitivity at 0.2 litres.
 - g) The FiO₂ is to be determined by the treating clinician and in keeping with unit protocol.
 - i) For infants who are in air and do not need require supplemental oxygen, saturations that are mostly above 90% are regarded as satisfactory.
 - ii) For infants who require supplemental oxygen, saturations should be targeted between 90% and 94% (with alarm limits set according to unit policy).
- 5) Give exogenous surfactant via endotracheal tube if not already given. The decision to further doses of surfactant rests with the treating clinician
- 6) Aim for minimal leak around the endotracheal tube. Consider repositioning or changing the endotracheal tube if the leak is ≥50%.
- 7) All pre-set and measured infant and ventilatory parameters are to be recorded by the nursing staff on the Neonatal Intensive Care nursing chart at hourly intervals according to standard unit protocol.
- 8) Blood gases:
 - a) These will be checked as frequently as is clinically indicated according to the infant's condition.
 - b) Gases will be arterial, or capillary if arterial access is not available.

- c) Aim to keep pH between 7.25-7.40, PaCO₂ 4.5 – 6.5 kPa (35-49mm Hg) and PaO₂ 7-10 kPa (50-75mm Hg). In the case of chronic dependency we will allow a degree of permissive hypercapnia PaCO₂ between 6-9kPa (45-68mmHg) provided that pH remains >7.20.
 - d) Do not allow the PaCO₂ to drop below 4kPa (30mmHg).
- 9) To maintain optimal ventilation and oxygenation whilst the infant remains on a ventilator, titrate the delivered volume (V_T) up or down in order to achieve satisfactory blood gases whilst **maintaining the expired tidal volume between 4-6mls/kg**.
- 10) All other interventions will be made according to unit protocol and at the discretion of the senior treating clinician.
- 11) Before weaning, administer a loading dose (20mg/kg) of caffeine citrate followed by a daily maintenance dose (5-10mg/kg).
- 12) If the infant's respiratory failure deteriorates ensure that equipment is functioning correctly and that ventilation and clinical management is optimised.
- a) If the infant's respiratory failure worsens despite optimisation strategies, high frequency oscillatory ventilation (HFOV) using the SensorMedics 3100A is an option if infant meets any of the following criteria for rescue treatment:
 - i) mean airway pressure ≥15 cmH₂O and FiO₂ ≥0.5 (50%) or
 - ii) oxygenation index (OI) >25 or
 - iii) intractable thoracic air leak or
 - iv) evidence of pulmonary hypertension with right to left shunt on echocardiogram
 - b) **The decision to change to HFOV must first be discussed with the Consultant Neonatologist on-call.**
 - c) The requirement to change to HFOV results in the infant exiting the study at that point. Analysis of that infant's data will be done on an intention-to-treat basis.
- 13) Weaning:
- a) Weaning will be commenced when the infant is stable with satisfactory blood gases and:
 - i) expired tidal volume 4.0 – 4.5mls/kg **and**
 - ii) peak inspiratory pressure ≤16cm H₂O **or** mean airway pressure <10cm H₂O **or** FiO₂ ≤0.35
 - b) Stop any sedative or muscle relaxant medications.
 - c) Ensure the infant has been loaded with caffeine citrate and maintenance doses have been started or are prescribed.
 - d) Keep the back up rate at 40 per minute.
 - e) When a mean airway pressure of 8cmH₂O is reached, decrease the back up rate to 30 per minute to assess respiratory drive and endurance of the baby.

- f) If stable switch to SIMV (volume mode) with pressure support. Adjust the pressure support dial on the ventilator to provide any spontaneous breaths with an inspired tidal volume of 4-6mls/kg.
- g) Subsequently decrease the set tidal volume and the pressure support to target an expired tidal volume of 4-4.5mls/kg with satisfactory blood gases and no increase in FiO_2 requirements
- h) Decrease SIMV rate to 20 per minute.
- i) If the infant does not breathe spontaneously or the blood gases or clinical status of the baby deteriorate, the infant should be put back onto volume assist-control ventilation at the settings that were used prior to changing to SIMV.

14) Extubation:

- a) Ensure that the infant is stable and achieving expired tidal volumes of 4 – 4.5mls/kg with satisfactory blood gases.
- b) When the infant maintains a mean airway pressure $<8\text{cmH}_2\text{O}$ and an $\text{FiO}_2 \leq 0.35$ for 6 consecutive hours perform a spontaneous breathing test (see Appendix C).
- c) If the spontaneous breathing test is successful, extubate the infant onto CPAP unless there is a specific clinical contraindication such as pulmonary air leak.
- d) If the spontaneous breathing test is unsuccessful, continue on the current ventilator parameters and repeat the test every 6 hours until it is successful.

15) Deterioration within 72 hours of extubation:

- a. The infant will be reintubated if any of the following are present (these criteria relate to the first two reintubations after the initial extubation):
 - i) $\text{FiO}_2 \geq 0.5$ for >2 consecutive hours to maintain oxygen saturations from 90-95%
or
 - ii) apnoea: one major apnoea (requiring mask ventilation) at any time or ≥ 6 minor apnoeas (associated with bradycardia and desaturation and requiring stimulation) in 6 consecutive hours, on a background of respiratory distress syndrome and despite giving a loading dose of caffeine citrate
or
 - iii) $\text{pCO}_2 > 8.5$ and $\text{pH} < 7.20$
- b. In this case the mode of ventilation that the infant was originally randomised to (ie: volume assist-control mode) should be used.

16) **NO CROSS OVER TO THE VG MODE OF VENTILATION IS ALLOWED DURING ANY FURTHER PERIOD OF VENTILATION.**

- 17) If the infant needs to be reintubated ≥ 72 hours after extubation **the mode of ventilation that the infants was originally assigned to (ie: volume assist-control mode) should be used. No cross-over to the VG arm is permitted.** The criteria used to reintubate at that time will be determined by the treating clinician.

Appendix 9.6 Caring for an infant randomised to VG

- 1) Written parental consent must be obtained within 36 hours of randomisation.
- 2) Pick a sealed opaque envelope from box according to appropriate gestational age group. Write the infant's name and hospital number on the envelope **before** opening it.
- 3) Infant is allocated to volume guarantee mode.
- 4) Select ventilator settings:
 - a) Mode:
 - i) Select the pressure assist control mode **AND** the volume guarantee mode and accept the mode.
 - b) Volume:
 - i) Use the volume dial to set the **initial** delivered volume at 4.5mls/kg. The number selected on the volume dial must equal the actual volume that infant is to receive (eg: to give 4.5mls/kg to a 1kg infant, set the number '4.5' on the volume dial; to give 4.5mls/kg to a 2kg infant, set the number '9' on the volume dial, etc)
 - ii) The volume can be increased or decreased subsequently to achieve acceptable blood gas results (see point 12).
 - c) Go to the Advanced Settings window and set the inspiratory pressure to 20 cmH₂O. This is a default inspiratory pressure that the ventilator will use for test breaths and as a back-up pressure during certain alarm conditions (such as during disconnection of the circuit or removal of the flow sensor). This is also the first inspiratory pressure used for the first volume that is delivered to the infant.
 - d) Press the Alarm Limits button and ensure that the 'High Ppeak' dial is set at 30cmH₂O
 - e) Set the positive end expiratory pressure (PEEP) to 4-6cmH₂O.
 - f) Set the back-up rate at 40 per minute.
 - g) Set the inspiratory time at 0.35 seconds.
 - h) Set the assist sensitivity at 0.2 litres.
 - i) The FiO₂ is to be determined by the treating clinician and in keeping with unit protocol:
 - i) For infants who are in air and do not need supplemental oxygen, saturations that are mostly above 90% are regarded as satisfactory.
 - ii) For infants who are in oxygen, saturations should be targeted between 90 and 94% (with alarm limits set according to unit policy)
- 5) Give exogenous surfactant via endotracheal tube if not already given. The decision to further doses of surfactant can be made by with the treating clinician.
- 6) Monitor the peak inspiratory pressure that is being generated with each breath (working PIP). Ensure that the 'High Ppeak' is set at 10cmH₂O above the working PIP. It can be increased to more than 30cmH₂O if this is needed to achieve an expired tidal volume of 4.5mls/kg.

- 7) If the machine delivers a display message saying '*Volume Guarantee Pressure is Limited*' or if the *Low V_T* or *Low V_{Te}* alarms sound, this means that the High Ppeak pressure is set too low.
 - a) If this occurs check the infant and the equipment and consult the troubleshooting guide.
 - b) If all mechanical and equipment problems have been excluded, it is likely that the High Ppeak pressure is set too low. Press the Alarm Limits button and increase the High Ppeak pressure to 10cmH₂O above the working PIP that is generated with each breath.
- 8) Aim for minimal leak around the endotracheal tube. Consider repositioning or changing the endotracheal tube if the leak is ≥50%.
- 9) All pre-set and measured infant and ventilatory parameters are to be recorded by the nursing staff on the Neonatal Intensive Care nursing chart at hourly intervals according to standard unit protocol.
- 10) Blood gases:
 - a) These should be checked as frequently as is clinically indicated according to the infant's condition.
 - b) Gases should be arterial, or capillary if arterial access is not available.
 - c) Aim to keep pH between 7.25-7.40, PaCO₂ 4.5 – 6.5 kPa (35-49mm Hg) and PaO₂ 7-10 kPa (50-75mm Hg). In the case of chronic dependency we will allow a degree of permissive hypercapnia PaCO₂ between 6-9kPa (45-68mmHg) provided that pH remains >7.20.
 - d) Do not allow the PaCO₂ to drop below 4kPa (30mmHg).
- 11) Increase or decrease the delivered volume in 0.5mls/kg increments as required to achieve acceptable blood gas results. **The delivered volume must be kept within the range of 4-6mls/kg.**
- 12) All other interventions should be made according to unit protocol and at the discretion of the senior treating clinician.
- 13) Before weaning, administer a loading dose (20mg/kg) of caffeine citrate followed by a daily maintenance dose (5-10mg/kg).
- 14) If the infant's respiratory failure deteriorates to ensure that equipment is functioning correctly and that ventilation and clinical management is optimised.
 - a) If the infant's respiratory failure worsens despite optimisation strategies, high frequency oscillatory ventilation (HFOV) using the SensorMedics 3100A is an option if infant meets any of the following criteria for rescue treatment:
 - i) mean airway pressure ≥15 cmH₂O and FiO₂ ≥0.5 (50%) or
 - ii) oxygenation index (OI) >25 or
 - iii) intractable thoracic air leak or
 - iv) evidence of pulmonary hypertension with right to left shunt on echocardiogram

- b) **The decision to change to HFOV must first be discussed with the Consultant Neonatologist on-call.**
- c) The requirement to change to HFOV results in the infant exiting the study at that point. Analysis of that infant's data will be done on an intention-to-treat basis.

15) Weaning:

- a) VG automatically weans the PIP as the infant's condition improves therefore the only parameters that will need to be weaned by the clinician are the delivered volume and the FiO_2 .
 - i) Stop any sedative and muscle relaxant medications.
 - ii) Ensure the infant has been loaded with caffeine citrate and maintenance doses have been started or are prescribed.
 - iii) Reduce the volume to 4-4.5mls/kg using the volume dial
 - iv) Keep the volume set at 4-4.5mls/kg as long as there are satisfactory blood gases and no increase in FiO_2 requirements.

16) Extubation:

- a) Ensure that the infant is stable and achieving expired tidal volumes of 4-4.5mls/kg with satisfactory blood gases.
- b) When the infant maintains a mean airway pressure $<8\text{cmH}_2\text{O}$ and an $\text{FiO}_2 \leq 0.35$ for 6 consecutive hours perform a spontaneous breathing test.
- c) If the spontaneous breathing test is successful, extubate the infant onto CPAP unless there is a specific clinical contraindication such as pulmonary air leak.
- d) If the spontaneous breathing test is unsuccessful, continue on the current ventilator parameters and repeat the test every 6 hours until it is successful.

17) Deterioration within 72 hours of extubation:

- a) The infant will be reintubated if **any** of the following are present (these criteria relate to the first two reintubations after the initial extubation):
 - i) $\text{FiO}_2 \geq 0.5$ for >2 consecutive hours to maintain oxygen saturations from 90-95%
or
 - ii) apnoea: one major apnoea (requiring mask ventilation) at any time **or** ≥ 6 minor apnoeas (associated with bradycardia and desaturation and requiring stimulation) in 6 consecutive hours, on a background of respiratory distress syndrome and despite giving a loading dose of caffeine citrate
or
 - iii) $\text{pCO}_2 > 8.5$ and $\text{pH} < 7.20$
- b) **In this case the mode of ventilation to which the infant was originally randomised (ie: VG) should be used.**

18) **NO CROSS OVER TO THE VG MODE OF VENTILATION IS ALLOWED DURING ANY FURTHER PERIOD OF VENTILATION.**

19) If the infant needs to be reintubated ≥ 72 hours after extubation **the mode of ventilation that the infants was originally assigned to (ie: volume assist-control mode) should be used. No cross-over to the VG arm is permitted.** The criteria used to reintubate at that time will be determined by the treating clinician.

Appendix 9.7 Example of a case record form

Case Record File

Form 3: Delivery details

Place of birth	JCUH Other level 3 hospital..... Other level 2 hospital..... Other level 1 hospital..... Other
Reason for delivery	SOL Fetal Maternal
Labour before delivery	Yes No
Onset of labour	SOL Induced N/A
Rupture of membranes before delivery (hours)	
Mode of delivery	Vaginal Em. LSCS
Presentation at delivery	Cephalic Breech
Date of birth	
Time of birth (24hr clock)	
Gender	Male Female
Gestational age at birth	
Single or multiple birth	Singleton Twins Triplet Quad
Birth order (if multiple pregnancy)	
Resuscitation at birth (events in delivery room)	None Oxygen IPPV CPAP Intubation Surfactant ECM Drugs Fluid bolus Dextrose bolus Blood Other
Apgar score at 1 minute	
Apgar score at 5 minutes	
Apgar score at 10 minutes	
Time HR >100bpm (mins)	
Time of first gasp (mins)	
Time of regular respirations (mins)	
Cord gases	Arterial pH pCO ₂ BE Venous pH pCO ₂ BE Not done
Other	

Appendix 9.8 Trial Oversight Report



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15th January 2016

Dear Helen and supervisory team

Re: Statistical report for a Randomised Controlled Trial Comparing Two Methods of Providing Volume-Targeted Ventilation in Preterm Infants with Respiratory Distress Syndrome: Volume Guarantee® Ventilation versus Volume-Controlled Ventilation

Thank you for asking me to independently review the progress and accumulating data on this trial as part of Good Clinical Practice. Dr Stocken (Head of Statistics Institute of Health and Society, Newcastle University) and I had a teleconference today to discuss the report, which had been emailed to me by Dr Wilkinson, a medical statistician in Dr Stocken's team. Dr Wilkinson had taken your trial and data and analysed as per your statistical analysis plan v0.6 and the results were reported to me blind for independent review. I confirm I was not provided with, nor requested the code break.

Dr Stocken updated me with trial progress since the analysis was carried out in September 2015. Recruitment to the trial is now closed and the trial patients are in follow-up. Data collection and data cleaning should be complete by March 2016. It is therefore timely to review the analysis plan and presentation of the data and make comment/ recommendations prior to unblinding.

First I would like to emphasise the importance of this study. You have designed a pragmatic trial to answer an important question in newborn infants. We know the advantage of volume targeted ventilation in newborns. Your study aims to directly compare 2 different methods of volume targeted ventilation. The question is, and remains, clinically relevant with a clinically relevant primary outcome of speed of weaning.

Congratulations on recruiting to target. The report is based on a snapshot of data from September based on 50 babies. I noted a small imbalance in maternal demographics, specifically the proportion of mothers receiving antenatal steroids. This is likely due to the small numbers but there is a small chance that any increased lung function could make the primary outcome be achieved more easily. It would be useful to address this in the analysis of the primary outcome.

I do not consider the imbalance noted of the proportion of babies born at trial site would affect the clinical outcomes. The small imbalance in non-invasive ventilation before intubation is not likely to be influential. I possibly would have expected more outborn than inborn babies but again this is a likely to be a chance finding.

I could not see the safety aspects, as described in the protocol, presented in the report. Safety is of paramount importance and I would expect to see data in terms of reported complications and mortality reported, to enable full clinical interpretation to the results. I would recommend this is updated accordingly in the analysis plan.

I reviewed the primary outcome data and confirm adequate follow-up for this outcome. The analyses are well presented. I was able to review the unadjusted analysis and the analysis adjusted

by the stratification factor at randomisation of gestational age. My only comment is in relation to the distribution of the primary outcome which I do not believe is likely to be normally distributed. The sample size calculation is based on a normal distribution and the impact of this should be commented on upfront in the discussion. Dr Stocken recommended that a retrospective calculation for log-rank analysis could be conducted. She explained this may influence the decision of what to present in the final analysis of the trial – hypothesis driven (p-value) or summary statistics (Hazard Ratio). Dr Stocken explained that for Good Clinical Practice, this decision should be made prior to the final analysis being undertaken and documented in an updated statistical analysis plan. I would recommend carrying this out and would be pleased to discuss any decisions further, by email, if that would be helpful.

One final comment is not in relation to the statistical report but in relation to the Appendix in the protocol. I noted the weaning strategies are different across the 2 arms and wondered the reasoning behind this. I believe it will be important to discuss this at presentation/ publication. Also the Appendix shows the volume control to be 4-6ml/kg and volume guarantee to be 4.5ml/kg. I would have expected these to be the same and would recommend discussion around this and any impact of this on mean area pressure.

I would like to congratulate Helen on undertaking an ambitious and important study and for recruiting to target. I believe Helen will have learned a great deal about clinical trials, the regulatory process and statistics and wish her well with her MD submission. I am pleased to have been able to review and comment on the trial progress through this independent review and have made some suggestions here. I believe the study is well conducted and will be publishable and would encourage Helen to discuss some of the issues raised here at publication to increase the chance of publication in a high impact journal.

With best wishes

Dr Jaideep Singh

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